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# RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL  
45TH YEAR—ESTABLISHED 1956

## **SPECIAL ISSUE**

### **LONG-TERM OXYGEN THERAPY PART I**

- Historical Highlights
- Pathophysiology and Clinical Effects of Chronic Hypoxia
- Adverse Effects of Low-Flow Oxygen Therapy
- Detection and Monitoring of Hypoxemia and Oxygen Therapy
- Delivery Systems
- Oxygen-Conserving Techniques and Devices
- Effects on Mortality and Morbidity
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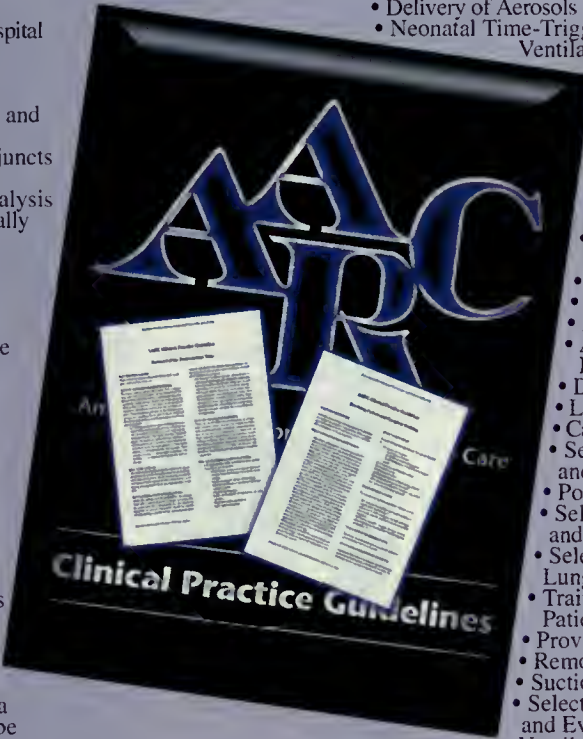
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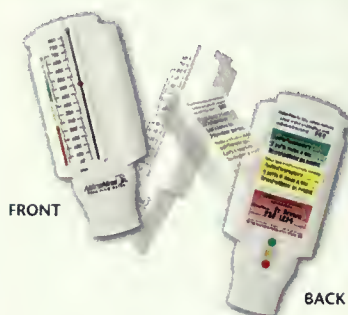
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## SPECIAL ISSUE

### STATE-OF-THE-ART CONFERENCE ON LONG-TERM OXYGEN THERAPY PART I

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Dasgupta A, Rice R, Mascha E, Litaker D, Stoller JK. Chest 1999 Aug;116(2):447-455.

**BACKGROUND:** In the context that special weaning units have been advocated as effective alternatives to the ICU for weaning selected patients, we initiated a Respiratory Special Care Unit (ReSCU) at the Cleveland Clinic Hospital in August 1993. The goals of the ReSCU were the following: (1) to wean ventilator-dependent patients when possible; and (2) when weaning was not possible, to optimize patient and family instruction for patients going home with ventilatory support. This study presents our 4-year experience with 212 patients managed in the ReSCU and analyzes clinical features associated with favorable clinical outcomes. **METHODS:** The features of the ReSCU include six private beds in a pulmonary inpatient ward staffed by nurses with special pulmonary expertise; 24-h respiratory therapy supervision; bedside and central noninvasive monitoring (i.e., continuous pulse oximetry, end tidal capnometry, and ventilator alarms); and a multidisciplinary approach involving dietitians, physical therapists, occupational therapists, social workers, and speech pathologists. All ReSCU patients were cared for primarily by a pulmonary/critical care attending physician and fellow, with consultative input solicited as deemed necessary. The criteria for admission to the ReSCU

included hemodynamic stability; absence of an arrhythmia requiring telemetry; and in the attending physician's judgment, the ability to benefit from the ReSCU. **RESULTS:** Between August 23, 1993, and August 31, 1997, 212 patients were admitted to the ReSCU. The median age was 68 years old; 55% were women; 86% were white; and 55% were transferred from the medical ICU. Underlying reasons for ventilator dependence were ARDS from a nonsurgical cause (33%), ARDS following surgery (18%), status post-cardiothoracic surgery (13%), status post-thoracic surgery (12%), and COPD (12%). The median length of ReSCU stay was 17 days (interquartile range, 10 to 29 days). Eighteen percent ( $n = 38$ ) died during the hospitalization. Among the 174 survivors, complete ventilator independence was achieved in 127 patients (60% of the 212 patient cohort), 28 patients were ventilator dependent (13% of 212 patients), and the remaining 19 patients (9%) required partial ventilatory support. Univariate analysis regarding the association of baseline characteristics with death identified lower albumin and transferrin levels, increasing age, and the physician's estimate of lower weaning likelihood as significant correlates of death. In contrast, achieving complete ventilator independence was associated with a higher serum albumin level, a nonmedical ICU referral source, a cause of respiratory failure other than COPD, and a physician's es-

timate of higher weaning likelihood. To analyze the financial impact of the ReSCU, we assumed that ReSCU patients would have otherwise stayed in the medical ICU and compared the charges (ICU vs ReSCU) with, for a subset of patients, the true costs of ReSCU vs. ICU care. Analyses of both charges and cost differences showed similar savings associated with ReSCU care (\$13,339 per patient [charges] and \$10,694 per patient [costs]). **CONCLUSIONS:** We conclude the following: (1) the rate of achieving complete ventilator independence in the ReSCU was high; and (2) based on our achieving clinical outcomes, which are comparable to the most favorable rates reported in other series from ventilator units, we conclude that the ReSCU can be an effective and cost-saving alternative to the ICU for carefully selected patients.

**Role of Different Routes of Tracheal Colonization in the Development of Pneumonia in Patients Receiving Mechanical Ventilation**—Cardenosa Cendrero JA, Sole-Violan J, Bordes Benitez A, Noguera Catalan J, Arroyo Fernandez J, Saavedra Santana P, Rodriguez de Castro F. Chest 1999 Aug;116(2):462-470.

**STUDY OBJECTIVE:** To evaluate the importance of the different pathogenic pathways involved in the development of ventilator-associ-

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ated pneumonia (VAP). DESIGN: Prospective study. SETTING: An 18-bed medical and surgical ICU. PATIENTS: One hundred twenty-three patients receiving mechanical ventilation (MV). INTERVENTIONS: Tracheal, pharyngeal, and gastric samples were obtained simultaneously every 24 h. In cases where VAP was suspected clinically, bronchoscopy with protected specimen brush and BAL were performed. Semiquantitative cultures of pharyngeal samples and quantitative cultures for the remaining samples were obtained. RESULTS: Tracheal colonization at some time during MV was observed in 110 patients (89%). Eighty patients had initial colonization, 34 patients had primary colonization, and 50 patients had secondary colonization. Nineteen patients had VAP, and 25 organisms were isolated. For none of these organisms was the stomach the initial site of colonization. Gram-positive organisms colonized mainly in the trachea during the first 24 h of MV ( $p < 0.001$ ). On the contrary, enteric Gram-negative bacilli ( $p < 0.001$ ) and yeasts ( $p < 0.002$ ) colonized the trachea secondarily. Previous endotracheal intubation ( $p < 0.005$ ) and acute renal failure before admission to the ICU ( $p < 0.001$ ) were associated with colonization by *Pseudomonas aeruginosa*; prior antibiotics were associated with colonization by *Acinetobacter baumannii* ( $p < 0.05$ ) and yeasts ( $p < 0.006$ ); and cranial trauma was associated with *Staphylococcus aureus* colonization ( $p < 0.035$ ). CONCLUSIONS: Although the stomach can be a source of organisms that colonize the tracheobronchial tree, it is a much less common source of the bacteria that cause VAP. The pattern of colonization and risk factors may be different according to the type of organisms involved.

**A Comprehensive Educational Program Improves Clinical Outcome Measures in Inner-City Patients with Asthma**—George MR, O'Dowd LC, Martin I, Lindell KO, Whitney F, Jones M, et al. Arch Intern Med 1999 Aug 9–23; 159(15):1710–1716.

**BACKGROUND:** Despite improved understanding of the pathophysiology of asthma, morbidity and mortality continue to rise, with disproportionate increases occurring among urban, indigent minorities. New approaches in the management of asthma are therefore necessary to reverse these dramatic and costly trends. **OBJECTIVE:** To determine if patients who are admitted to the hospital with acute asthma and receive inpatient education will have improved outpatient follow-up and clinical outcome measures compared with those receiving conventional care. **METHODS:** Patients enrolled in the study had a primary admission diagnosis of asthma and were between ages 18 and 45 years. Exclusion criteria included comorbid disease, inability to speak English, absence of a telephone in the primary residence, or pregnancy.

Seventy-seven patients admitted from the emergency department with asthma were randomized to either the inpatient educational program (IEP) or routine care (control group). Patients in the IEP received asthma education, bedside spirometry, a telephone call 24 hours after discharge, and scheduled follow-up in an outpatient asthma program within 1 week of discharge. Those individuals randomized to the routine management group received conventional inpatient asthma care and routine follow-up. **RESULTS:** The patients enrolled in the IEP had a markedly higher follow-up rate compared with outpatient appointments (60% vs. 27%;  $p = 0.01$ ) and significantly fewer emergency department visits ( $p = 0.04$ ) and hospitalizations ( $p = 0.04$ ) for asthma in the 6 months following IEP intervention, as compared with control patients. This represented a substantial cost savings to the managed care organization. **CONCLUSION:** Our study suggests that an IEP in the treatment of indigent, inner-city patients hospitalized with asthma reduces the need for subsequent emergent care and improves outpatient follow-up in a cost-effective manner.

**Effects of Continuous Negative Airway Pressure on Lung Volume and Respiratory Resistance**—Lorino AM, Hamoudi K, Lofaso F, Dahan E, Mariette C, Harf A, Lorino H. J Appl Physiol 1999 Aug;87(2):605–610.

This study was designed to determine the responses of lung volume and respiratory resistance (Rrs) to decreasing levels of continuous negative airway pressure (CNAP). Twenty normal subjects were studied in the basal state and under CNAP levels of -5, -10, and -15 hPa. Rrs was measured by the forced oscillation technique (4–32 Hz). End-expiratory lung volume (EELV) and tidal volume ( $V_T$ ) were measured by whole body plethysmography. Rrs was extrapolated to 0 Hz (R(0)) and estimated at 16 Hz (R(16)) by linear regression analysis of Rrs vs. frequency. Specific Rrs, SR(0) and SR(16), were then calculated as R(0) (EELV +  $V_T/2$ ) and R(16) (EELV +  $V_T/2$ ), respectively. EELV significantly decreased, whereas R(0), R(16), SR(0), and SR(16) significantly increased, as the CNAP level decreased ( $p < 0.0001$  for all). At the lowest CNAP level, R(0) and R(16) reached  $198 \pm 13$  and  $175 \pm 9\%$  of their respective basal values. The CNAP-induced increase in R(0) was significantly higher than that in R(16) ( $p < 0.004$ ). Our results demonstrate that the CNAP-induced increase in Rrs does not result from a direct lung volume effect only and strongly suggest the involvement of other factors affecting both intrathoracic and extrathoracic airway caliber.

**Daytime Blood Pressure Elevation After Nocturnal Hypoxia**—Arabi Y, Morgan BJ, Good-

man B, Puleo DS, Xie A, Skatrud JB. *J Appl Physiol* 1999 Aug;87(2):689-698.

The purpose of this study was to investigate whether nocturnal hypoxia causes daytime blood pressure (BP) elevation. We hypothesized that overnight exposure to hypoxia leads the next morning to elevation in BP that outlasts the hypoxia stimulus. We studied the effect on BP of two consecutive night exposures to hypobaric hypoxia in 10 healthy normotensive subjects. During the hypoxia nights, subjects slept for 8 h in a hypobaric chamber at a simulated altitude of 4,000 m (barometric pressure = 462 mm Hg). Arterial O<sub>2</sub> saturation and electrocardiogram were monitored throughout the night. For 30 min before the nocturnal simulated ascent and for 4 h after return to baseline altitude the next morning, BP was measured every 5 min while the subject was awake. The same measurements were made before and after 2 normoxic nights of sleep in the hypobaric chamber at ambient barometric pressure (745 mm Hg). Principal components analysis was applied to evaluate patterns of BP response after the second night of hypoxia and normoxia. A distinct pattern of diastolic BP (DBP) elevation was observed after the hypoxia night in 9 of the 10 subjects but in none after the normoxia night. This pattern showed a mean increase of 4 mm Hg in DBP compared with the presleep-awake baseline in the first 60 min and a return to baseline by 90 min. We conclude that nocturnal hypoxia leads to a carryover elevation of daytime DBP.

**Does Noninvasive Ventilation Reduce the ICU Nosocomial Infection Risk? A Prospective Clinical Survey**—Nouridine K, Combes P, Carton MJ, Beuret P, Cannamela A, Ducreux JC. *Intensive Care Med* 1999 Jun;25(6):567-573.

**OBJECTIVE:** To observe the nosocomial infection (NI) distribution in ventilated patients of a single intensive care unit (ICU) according to the kind of control of the upper airways: noninvasive positive pressure ventilation (NPPV) versus endotracheal intubation (ETI). **SETTING:** ICU of a general hospital. **DESIGN:** Prospective clinical and epidemiologic survey. **PATIENTS:** In the period December 1994-March 1997, 761 patients were included who needed mechanical ventilation for more than 48 h: 129 were ventilated by NPPV (NPPV group), 607 were intubated (ETI group) and 25 required intubation after a period of NPPV (NPPV-ETI group). **MEASUREMENTS AND RESULTS:** The data used were prospectively collected according to the NI epidemiologic surveillance protocol of "C. CLIN Sud Est, Rea Sud Est", France. NI included a ventilator-associated pneumonia (VAP), catheter-related infection, urinary tract infection and bacteremia. Occurrence of NI was estimated by the density

of incidence. Covariate-adjusted NI and VAP risk factors were assessed by the Cox model. The incidence density of total NI was lower for NPPV than for ETI (14.2 versus 30.3 per 1000 patient-days,  $p < 0.01$ ). The Cox model showed that the use of noninvasive ventilation, adjusted to the severity of illness (SAPS II), reduced not only the VAP risk (hazard ratio (HR) = 4.07) but also the NI risk (HR = 1.95). **CONCLUSION:** The use of NPPV reduces the risk of VAP and NI, compared to ETI, irrespective of the severity of the patient's illness.

**Validation of "Nine Equivalents of Nursing Manpower Use Score" on an Independent Data Sample**—Rothen HU, Kung V, Ryser DH, Zurcher R, Regli B. *Intensive Care Med* 1999 Jun;25(6):606-611.

**OBJECTIVE:** To compare the recently developed "nine equivalents of nursing manpower use score" (NEMS) with the simplified Therapeutic Intervention Scoring System (TISS-28). **DESIGN:** Prospective single centre study. **SETTING:** Adult 30-bed medical-surgical intensive care unit (ICU) in a tertiary care university hospital. **PATIENTS:** Data from all patients admitted in 1997 to the ICU were included in the study. **METHODS AND RESULTS:** NEMS and TISS-28 items were recorded prospectively for each nursing shift. There were three shifts per day. The Simplified Acute Physiology Score (SAPS) II was calculated for the first 24 h of ICU stay and each patient's basic demographic data were collected. The agreement between NEMS and TISS-28 was assessed by calculating the mean difference and the standard deviation of the differences between the two measures. Further, regression techniques and Pearson's correlation were used. Altogether, 2743 patients with a total of 28,220 nursing shifts were included; 62% of the shifts were used for postoperative/trauma patients and 38% for medical patients. Mean NEMS was  $26.0 \pm 8.1$  and mean TISS-28 was  $26.5 \pm 7.9$ . The scores differed by  $\leq 3$  points in 49 % of all shifts. The bias was  $-0.5 \pm 5.3$  (95% confidence interval  $-0.47$  to  $-0.60$ ) and the limits of agreement were  $-11.1$  to  $+10.1$ . The relation between the two systems was  $NEMS = 4.7 \pm 0.8 \times TISS-28$  ( $r = 0.78$ ,  $r^2 = 0.62$ ,  $p < 0.001$ ). Including postoperative/trauma patients only:  $NEMS = 1.9 \pm 0.9 \times TISS-28$ , for medical patients this equation was:  $NEMS = 6.0 \pm 0.8 \times TISS-28$ . First-day SAPS II explained 11% of the variability in first-shift NEMS and 5% of the variability in first-shift TISS-28. **CONCLUSIONS:** This study confirms a good agreement between TISS-28 and NEMS in a large, independent sample. However, as shown by the differences between medical and postoperative/trauma patients, a change in case mix may result in different regression equations. Further, wide limits of agreement indicate that there may be a

rather large variability between the two measures at the individual level.

**Oro- and Nasogastric Tube Passage in Intubated Patients: Fiberoptic Description of Where They Go at the Laryngeal Level and How to Make Them Enter the Esophagus**—Ozer S, Benumof JL. *Anesthesiology* 1999 Jul;91(1):137-143.

**BACKGROUND:** Insertion of a gastric tube (GT) in anesthetized, paralyzed, and intubated patients can be difficult. The purpose of this study was to determine fiberoptically why GTs succeed or fail to enter the esophagus and, based on these findings, to determine a mechanism for converting failures into successes. **METHODS:** Sixty patients under general anesthesia and orotracheally intubated were studied. The larynx and hypopharynx of each patient were viewed via a fibroscope placed through the left naris. GTs were passed orally (OGT) and nasally (NGT) in all patients, and the pathway of passage or site of resistance was visualized. In cases of resistance, medially directed ipsilateral neck pressure was applied over the lateral thyrohyoid membrane (termed lateral neck pressure) to try to allow passage of the GT. **RESULTS:** All 60 patients had both an OGT and NGT passed for a total of 120 attempts. The GT passed easily on the first attempt in 92 of 120 insertions (77%) (for OGT 51/60 = 85% and for NGT 41/60 = 68%,  $p < 0.05$ ). In 92% of these first-pass successes, the GT entered the hypopharynx just lateral to the arytenoid cartilages. The GT met resistance and failed to pass in 28 of 120 insertions (23%) (for OGT 9/60 = 15% and for NGT 19/60 = 32%). The sites of impaction were the piriform sinuses (13/28 = 46%), arytenoid cartilages (7/28 = 25%), and trachea (6/28 = 21%), and two OGTs did not pass the oropharynx (2/28 = 70%). Lateral neck pressure was attempted 20 times (for the piriform sinus and arytenoid cartilage impactions) with 17 successes (85%) and three failures (15%). The average distance to passage of the OGT and NGT by the arytenoid cartilage was 13.2 and 16.2 cm, respectively. **CONCLUSION:** GTs enter the hypopharynx just lateral to the arytenoid cartilages. Consequently, the most common sites of resistance at the laryngeal level are the arytenoid cartilages and piriform sinuses. Lateral neck pressure compresses the piriform sinuses and moves the arytenoid cartilages medially, relieving 85% of these GT impactions.

**A Matter of Life and Death: What Every Anesthesiologist Should Know About the Medical, Legal, and Ethical Aspects of Declaring Brain Death**—Van Norman GA. *Anesthesiology* 1999 Jul;91(1):275-287.

Accurate criteria for death are increasingly important as it becomes more difficult for the public to distinguish between patients who are still

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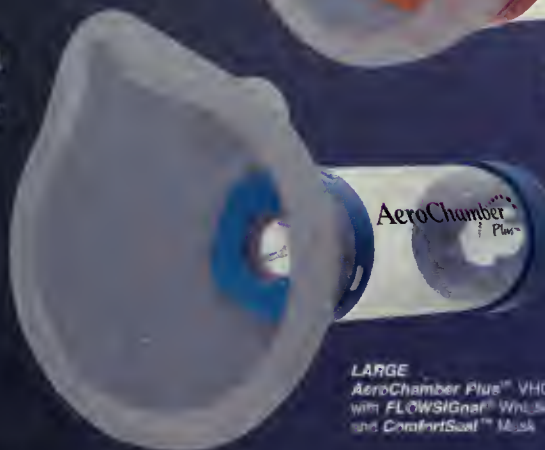
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alive from those who, through the aid of medical technology, merely look like they are alive even though they are dead. Patients and their families need to know that a clear line can be drawn between life and death, and that patients who are alive will not be unintentionally treated as though they are dead. For the public to trust the pronouncements of medical doctors as to whether a patient is dead or alive, the criteria must be unambiguous, understandable, and infallible. It is equally important to physicians that accurate, infallible criteria define death. Physicians need to know that a clear line can be drawn between life and death so that patients who are dead are not treated as though they are alive. Such criteria enable us to terminate expensive medical care to corpses. Clear criteria for death also allow us to ethically request the gift of vital organs. Clear, infallible criteria allow us to assure families and society that one living person will not be intentionally or unintentionally killed for the sake of another. The pressure of organ scarcity must not lead physicians to allow the criteria for life and death to become blurred because of the irreparable harm this would cause to the patient-physician relationship and the devastating impact it could have on organ transplantation. As the cases presented here illustrate, anesthesiologists have an important responsibility in the process of assuring that some living patients are not sacrificed to benefit others. Criteria for declaring death should be familiar to every anesthesiologist participating in organ retrieval. Before accepting the responsibility of maintaining a donor for vital organ collection, the anesthesiologist should review data supplied in the chart supporting the diagnosis of brain death and seriously question inconsistencies and inadequate testing conditions. Knowledge of brain death criteria and proper application of these criteria could have changed the course of each of the cases presented.

**Objectives, Methods and Content of Patient Education Programmes for Adults with Asthma: Systematic Review of Studies Published Between 1979 and 1998** (review)—Sudre P, Jacquemet S, Uldry C, Perneger TV. *Thorax* 1999 Aug;54(8):681–687.

**BACKGROUND:** Education programmes for adults with asthma vary widely. Such variability suggests a lack of consensus on what works and what does not. The objectives of this paper are to describe asthma education programmes and assess their variability. **METHODS:** A systematic review of reports published between 1979 and 1998 was conducted. Medline, the CINAHL database, the PsycINFO database, the Cochrane collaboration database, the Dissertation Index database, and cross referencing were used to identify educational interventions; 77 projects including 94 interventions that involved 7953 patients were analysed. A standard form

was used to record characteristics of studies (design, setting, size, year, and country of publication), projects (theoretical framework, objectives), and education (methods, duration, intensity, educator, and content). **RESULTS:** Most reports did not specify the general (56%) and educational objectives (60%) of the intervention. Important training characteristics were often not available: duration of education (45%) and number of sessions (22%), who delivered education (15%), whether training was conducted in groups or was individualised (28%). When this information was available there were wide variations in training methods and content: training duration ranged from 0 (self-education) to 58 hours and the number of sessions from 0 to 36; training tools such as peak flow meters, diary cards or books were used in various proportions of interventions (19%, 27%, and 23%, respectively). The content of education also differed widely between programmes. **CONCLUSIONS:** Insufficient documentation of asthma education programmes for adults precludes their replication. This, together with excessive variability, reduces the possibility of identifying their most effective components. A more systematic description of asthma training programmes should be promoted.

**Prevalence of Depression in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review** (review)—van Ede L, Yzermans CJ, Brouwer HJ. *Thorax* 1999 Aug; 54(8):688–692.

**BACKGROUND:** Patients with chronic obstructive pulmonary disease (COPD) have repeatedly been characterised as a population of chronically ill patients with a higher than normal prevalence of depression. Susceptibility for depression has been noted in patients with certain other chronic conditions. This systematic review was conducted to achieve a more definite answer to the question: do patients with COPD show a higher than normal prevalence of depression? **METHODS:** Studies in English language journals were retrieved by an electronic search over the period from 1966 to December 1997 and by an extended search of reference lists, and were included or excluded according to a system of diagnostic and methodological criteria. **RESULTS:** Ten studies were included, of which only four had a case-control design. Three of the case-control studies reported an increased prevalence of depression among patients with COPD which was statistically significant in only one. The fourth controlled study found a significantly increased depression score among COPD patients. Of the remaining six uncontrolled studies three found a high baseline prevalence of depression among their study group. **CONCLUSIONS:** An association between COPD and depression was found in the four controlled studies. The two methodologically best conducted studies that did

not detect a statistically significant higher prevalence lacked power. The two studies that did find a significant association used a questionable depression measure. The prevalence of depression was high compared with general population figures in three of six non-controlled studies. The empirical evidence for a significant risk of depression in patients with COPD remains inconclusive, due to the poor methodological quality of most of the published studies, the lack of studies with an adequate sample size, and variability in instruments and cut off scores used to measure depression.

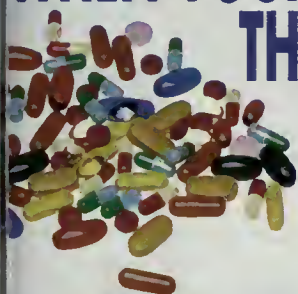
**Effect of High Versus Low Ambient Humidity on the Severity of Obstructive Sleep Apnoea**—Jokic R, Bhagchandani L, Zintel T, Baetz M, Fitzpatrick MF. *Thorax* 1999 Aug; 54(8):711–713.

**BACKGROUND:** Surface tension forces appear to make a significant contribution to upper airway closure in patients with obstructive sleep apnoea (OSA). It is possible that drying of the upper airway mucosa at night might contribute to these surface tension forces and the severity of OSA might therefore change with alteration of the ambient humidity. **METHODS:** A randomised single blind crossover study of high ambient relative humidity (HRH) versus low ambient relative humidity (LRH) was performed in 12 men of mean (SD) age 49 (9) years with mild OSA (apnoea/hypopnoea index (AHI) 14 (5.2)). On one night patients slept in continuous HRH (85 (4)%, range 80–93%) and on the other in LRH (16 (4)%, range 11–22%). **RESULTS:** The AHI was similar on the HRH and LRH nights (mean difference 3; 95% CI -2 to 9,  $p = 0.20$ ) and no statistically significant differences in AHI were observed on the two nights after standardising for body position and sleep stage. Sleep stage distribution and the proportion of time spent in the supine position were similar on the HRH and LRH nights. The number of non-respiratory arousals was also similar on the two nights. **CONCLUSION:** Altering ambient humidity alone has no significant impact on the severity of OSA.

**Increase in Admission Threshold Explains Stable Asthma Hospitalization Rates**—Russo MJ, McConnochie KM, McBride JT, Szilagyi PG, Brooks AM, Roghmann KJ. *Pediatrics* 1999 Sep;104(3 Pt 1):454–462.

**BACKGROUND:** Asthma morbidity and mortality has increased substantially in recent years, but asthma hospitalization rates among many geographic and sociodemographic groups have remained stable. Observations on asthma hospitalization rates and severity of acute episodes might provide valuable insight into the functioning of the health care system during this period of health care reform. **OBJECTIVE:** To

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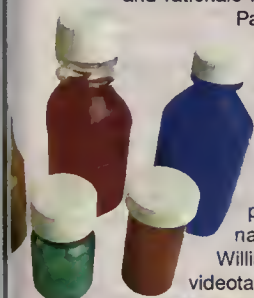
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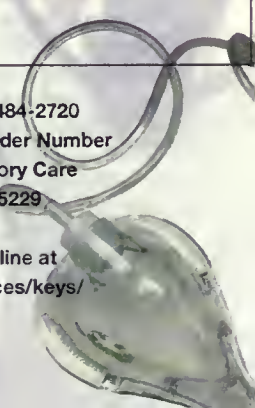
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analyze changes between 1991 and 1995 in childhood asthma hospitalization rates and severity of acute episodes. **DESIGN AND METHODS:** All 29,329 hospitalizations, including 2028 for asthma, for the 198,893 children (<19 years of age) in Monroe County (Rochester), New York, were studied during this 5-year period. Severity was determined by hospital record review on a 22% random sample. Using the worst oxygen saturation ( $S_{aO_2}$ ) during the first 24 hours of hospitalization as the primary index of severity, episodes were categorized as mild (0 to  $\geq 95$ ), moderate (90 to 94), or severe (<90). **RESULTS:** Hospitalization rates are expressed as hospitalizations per 1000 child-years. The overall asthma hospitalization rate was 2.04 (95% confidence interval, 1.95–2.13). The overall annual asthma hospitalization rate remained relatively stable from 1991 (1.90) to 1995 (2.31), whereas the hospitalization rates for severe asthma rose 270%—from 0.57 to 1.55—during this period. Simultaneously, the hospitalization rates for mild asthma decreased from 0.26 to 0.12. As a proportion of all asthma hospitalizations between 1991 and 1995, severe episodes increased from 31.5% to 60.4%; conversely, mild episodes decreased from 14.1% to 4.7%. **CONCLUSIONS:** Severity increased significantly among children hospitalized for asthma while the overall asthma hospitalization rate remained stable. It seems that the health care system in this community has responded to an increase in severity of asthma by raising the severity threshold for admission.

**Cardiopulmonary Resuscitation in the Very Low Birth Weight Infant: The Vermont Oxford Network Experience**—Finer NN, Horbar JD, Carpenter JH. *Pediatrics* 1999 Sep;104(3 Pt 1):428–434.

**OBJECTIVE:** The limited literature available to date suggests that the use of delivery room cardiopulmonary resuscitation (DR-CPR) is associated with very poor outcomes, especially for extremely low birth weight infants. We reviewed the cumulative experience of the Vermont Oxford Network to determine the actual utilization of DR-CPR and the neonatal outcomes of such infants. **METHODS:** A retrospective review of information available in the Vermont Oxford Network Database for the years 1994 to 1996. The data set was collected from 196 neonatal units who participate in the Network (data for infants 401 to 500 g were from 1996 only). Infants were eligible for study if they received DR-CPR defined as the administration of chest compressions and/or epinephrine in the delivery room as noted on the Vermont Oxford Network Database record. **RESULTS:** Information regarding survival was available for 27,707 newborns with birth weights from 501 to 1500 g, and 497 infants with birth weights from 401 to 500 g. There were 24,001 (86.6%) survivors. Overall DR-CPR was given

to 9.3% of infants from 401 to 500 g and 6% of infants from 501 to 1500 g, 82.1% receiving chest compressions, and 66.7% receiving epinephrine. Survival of infants receiving DR-CPR was 23.9% for infants of 401 to 500 g, and 63.3% for infants of 501 to 1500 g, compared with 16.7% and 87.9% for infants in these weight groups not receiving DR-CPR. Survival was greater for infants of 501 g or greater without DR-CPR compared with those who received this intervention within each 250-g birth weight subgroup. For infants of <1000 g, survival was 53.8% with DR-CPR compared with 74.9% without. Head ultrasounds were available for 95.5% of all surviving infants and 96.7% of infants who received DR-CPR. Overall, any grade of intraventricular hemorrhage (IVH) occurred more frequently in infants who received DR-CPR (38%) than in those who did not (21%). Grade 3 or 4 (severe) IVH was seen in 15.3% of infants who received DR-CPR compared with 4.9% of the infants who did not. Overall, survival without severe IVH occurred in 52.2% of DR-CPR infants compared with 81.3% of infants who did not require this intervention. **CONCLUSION:** The majority of very low birth weight and extremely low birth weight infants who receive DR-CPR survive, and at least half of such infants who survive do not have evidence of severe IVH. Further follow-up studies are required to determine the long-term neurodevelopmental outcome of such infants. The current study does not support the previously noted poor outcome in extremely low birth weight infants who receive DR-CPR.

**Lack of Influence of Gender on Outcomes of Mechanically Ventilated Medical ICU Patients**—Epstein SK, Vuong V. *Chest* 1999 Sep;116(3):732–739.

**STUDY OBJECTIVES:** Recent studies combining medical and surgical patients have suggested that mortality is higher for mechanically ventilated women than for men. This study was designed to determine whether there are gender-based differences in outcomes in mechanically ventilated medical ICU (MICU) patients. **DESIGN AND SETTING:** Prospective observational study in an MICU of a tertiary-care academic medical center. **PATIENTS:** Five hundred eighty consecutive patients admitted to the MICU service and mechanically ventilated for a minimum of 12 h. **RESULTS:** There was no difference in overall hospital mortality rate (woman, 36.3%; men, 40.4%;  $p > 0.2$ ). No differences in mortality rates were noted after stratification based on age, underlying comorbid condition, APACHE (acute physiology and chronic health evaluation) II score, indication for mechanical ventilation, or acute hepatic or renal failure. Using a multiple logistic regression model, gender was not independently associated with hospital mortality. No differences were found between men and women for a num-

ber of secondary outcomes, including likelihood of undergoing weaning trials, success of weaning trials, time between onset of mechanical ventilation and extubation, total time on mechanical ventilation, rate of unplanned extubations, need for reintubation or tracheostomy, or duration of MICU and hospital stay, after the onset of mechanical ventilation. The number and timing of orders written to withhold care were comparable between men and women. **CONCLUSIONS:** Using univariate and multivariate analyses, we found no differences in hospital mortality rates between mechanically ventilated men and women. Differences in the process of care or gender-based treatment bias may explain previously reported differences in outcomes.

**Underdiagnosis and Undertreatment of Asthma in the Elderly. Cardiovascular Health Study Research Group**—Enright PL, McClelland RL, Newman A, Gottlieb DJ, Lebowitz MD. *Chest* 1999 Sep;116(3):603–613.

**OBJECTIVE:** To describe the clinical correlates of asthma in a community-based sample of elderly persons. **PARTICIPANTS:** A community sample of 4,581 persons  $\geq 65$  years old from the Cardiovascular Health Study. **MEASUREMENTS:** Standardized respiratory, sleep, and quality-of-life (QOL) questions, a medication inventory, spirometry, and ambulatory peak flow. **RESULTS:** Four percent of the participants reported a current diagnosis of asthma (definite asthma), while another 4% reported at least one attack of wheezing accompanied by chest tightness or dyspnea during the previous 12 months (probable asthma). Smokers and those with congestive heart failure were excluded from the subsequent analyses, leaving 2,527 participants. Of those who had definite asthma, 40% were taking a sympathomimetic bronchodilator, 30% inhaled corticosteroids, 21% theophylline, and 18% oral corticosteroids; 39% were taking no asthma medications. The participants with definite or probable asthma were much more likely than the others to have a family history of asthma, childhood respiratory problems, a history of workplace exposures, dyspnea on exertion, hay fever, chronic bronchitis, nocturnal symptoms, and daytime sleepiness. They were also more likely to report poor general health, symptoms of depression, and limitation of activities of daily living. There was little difference in the morbidity and QOL of participants with recent asthma-like symptoms who had received the diagnosis of asthma versus those who had not. **CONCLUSIONS:** Asthma in elderly persons is associated with a lower QOL and considerable morbidity when compared with those who do not have asthma symptoms. Asthma is underdiagnosed in this group and is often associated with allergic triggers; inhaled corticosteroids are underutilized.



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## Helping you heal.

**Analysis of Tracheal Sounds during Forced Exhalation in Asthma Patients and Normal Subjects: Bronchodilator Response Effect—**Fiz JA, Jane R, Salvatella D, Izquierdo J, Lores L, Caminal P, Morera J. *Chest* 1999 Sep;116(3):633–638.

**PURPOSE:** During the past 10 years, the acoustic analysis of breath sounds has been used as a diagnostic tool in patients suffering from obstructive respiratory diseases. Acoustic analysis might be able to monitor the response to bronchodilator therapy in a clinical setting. So far, few studies have been carried out in asthmatic patients. To assess the responses of a sampling of asthma patients to an inhaled bronchodilator (terbutaline) by means of spectral analysis of the tracheal sound performed during forced expiratory maneuvers. **MATERIAL AND METHODS:** Seventeen nonsmoking asthma patients (9 were male, 8 were female) who had been suffering from the disease for  $\geq 15$  years were included in the study, as were 15 normal subjects (7 were male, 8 were female). The average age ( $\pm$  SD) was  $56.5 \pm 15.2$  years (FVC,  $2.7 \pm 0.9$  L [63.4%]; FEV<sub>1</sub>,  $1.5 \pm 0.6$  L [53.0%]). The tracheal sounds were collected during three forced expiratory maneuvers with a sampling frequency of 5,000 Hz and were analyzed by applying a 16-parameter autoregressive model. **RESULTS:** The centroid frequency decreased after the bronchodilator was given at different flow segments between 1.2 and 0.4 L/s, with significant changes between 0.6 and 0.4 L/s. **CONCLUSIONS:** Patients with asthma showed changes in the spectral acoustic analysis frequencies after the administration of a bronchodilator drug (terbutaline) during forced expiratory maneuvers.

**A Method for the Standardized Offline Collection of Exhaled Nitric Oxide—**Silkoff PE, Stevens A, Pak J, Bucher-Bartelson B, Martin RJ. *Chest* 1999 Sep;116(3):754–759.

**STUDY OBJECTIVES:** Exhaled nitric oxide (ENO) is a noninvasive marker of airway inflammation. The purpose of this study was to compare a standardized offline ENO measurement apparatus with a validated on-line method. **DESIGN:** Asthmatic volunteers ( $n = 21$ ) had ENO measured by the two following methods: (1) inhalation to total lung capacity (TLC) followed by exhalation at a constant flow (45 mL/s) against a high resistance, while monitoring nitric oxide (NO) and pressure on-line; and (2) inhalation to TLC and exhalation into mylar balloons via an apparatus that included the same resistance and flow rate as used in the on-line method. We also examined NO stability in mylar balloons over 48 h. **MEASUREMENTS AND RESULTS:** ENO values (given as geometric mean in parts per billion [ppb]; 95% confidence intervals) differed between the on-line method (69.6; 42.6 to 113.8) and the off-

line method (49.5; 30.9 to 79.3), indicating that the offline method gave lower ENO measures than the on-line method ( $p < 0.001$ ). Furthermore, this difference between measures increased with increasing mean values. The intraclass correlation coefficient (0.931), however, showed excellent correlation between the on-line and offline methods. Within-subject repeatability, as assessed by the coefficient of repeatability (CR), was good for both the on-line and offline methods (CR, 1.09 and 1.17, respectively). Geometric mean NO concentrations (95% confidence limits) in mylar balloons containing exhalate increased from a baseline of 55.8 ppb (36.9, 84.4) to 64.5 ppb (45.6, 91.1) and 69.5 ppb (51.4, 94.0) at 24 h and 48 h, respectively. **CONCLUSIONS:** The offline method gave reproducible ENO values that were consistently smaller than, but showed good correlation with, values obtained with on-line ENO collection. This method is suitable for offline collection, but the measured values are not interchangeable with those obtained by on-line measurement.

**Hypoxemia and Hypercapnia during Exercise and Sleep in Patients with Cystic Fibrosis—**Bradley S, Solin P, Wilson J, Johns D, Walters EH, Naughton MT. *Chest* 1999 Sep;116(3):647–654.

**BACKGROUND:** In patients with cystic fibrosis (CF), it has been proposed that hypoxemia and hypercapnia occur during episodes of stress, such as exercise and sleep, and that respiratory muscle weakness because of malnutrition may be responsible. **METHODS:** Pulmonary function, respiratory muscle strength, and nutrition were assessed and correlated with the degree of hypoxemia and hypercapnia during exercise and sleep in 14 patients with CF and 8 control subjects. **RESULTS:** Despite no differences in maximum static inspiratory pressure ( $PI_{max}$ ) between the two groups, the CF group developed more severe hypoxemia (minimum oxyhemoglobin saturation [ $S_{pO_2}$ ],  $89 \pm 5\%$  vs  $96 \pm 2\%$ ;  $p < 0.001$ ) and hypercapnia (maximum transcutaneous  $CO_2$  tension [ $PtcCO_2$ ],  $43 \pm 6$  vs  $33 \pm 7$  mm Hg;  $p < 0.01$ ) during exercise. Similarly, during sleep, the CF group developed greater hypoxemia (minimum  $S_{pO_2}$ ,  $82 \pm 8\%$  vs  $91 \pm 2\%$ ;  $p < 0.005$ ), although  $CO_2$  levels were not significantly different (maximum  $PtcCO_2$ ,  $48 \pm 7$  vs  $50 \pm 2$  mm Hg). Within the CF group, exercise-related hypoxemia and hypercapnia did not correlate with FEV<sub>1</sub>, residual volume/total lung capacity ratio (RV/TLC),  $PI_{max}$ , or body mass index (BMI). Hypoxemia and hypercapnia during sleep correlated with markers of gas trapping (RV vs minimum arterial oxygen saturation [ $r = -0.654$ ;  $p < 0.05$ ]), RV vs maximum  $PtcCO_2$  ( $r = 0.878$ ;  $p < 0.001$ ), and RV/TLC vs maximum  $PtcCO_2$  ( $r = 0.790$ ;  $p < 0.01$ ) but not with  $PI_{max}$  or BMI. **CONCLUSION:** Patients with moderately severe CF de-

velop hypoxemia and hypercapnia during exercise and sleep to a greater extent than healthy subjects with similar respiratory muscle strength and nutritional status. Neither respiratory muscle weakness nor malnutrition are necessary to develop hypoxemia or hypercapnia during exercise or sleep.

**Intubation and Mechanical Ventilation for COPD: Development of an Instrument to Elicit Patient Preferences—**Dales RE, O'Connor A, Hebert P, Sullivan K, McKim D, Llewellyn-Thomas H. *Chest* 1999 Sep;116(3):792–800.

**BACKGROUND:** Whether to simply provide palliative care or to intubate and use mechanical ventilation (MV) in a patient with severe COPD in acute respiratory failure is a difficult decision. The outcome of MV cannot be accurately predicted. Some patients cannot be weaned from the ventilator; those who are weaned often return to chronic severe respiratory disability. It is important that patients participate in this decision, but assistance is required. To address these issues, we developed and pilot-tested an aid to assist patients with MV decisions. **METHODS:** A scenario-based decision aid was developed consisting of an audiocassette and a booklet describing intubation and MV and its possible outcomes. We used a probability tradeoff technique to elicit the patients' preferences and a decisional conflict scale to evaluate satisfaction. **RESULTS:** With the assistance of the decision aid, all patients (10 men and 10 women) reached a decision. Two men and all 10 women declined MV. Mean decisional conflict was low (2.2 of a possible 5; SD, 0.9). At 1 year, only two patients (11%) had changed their decision. The agreement between physicians and patients was 65%; between next-of-kin and patients, there was uniform disagreement. **CONCLUSION:** With the decision aid, stable decisions were made with satisfaction and confidence. Proxy decisions were incongruent, especially when made by family members. The strong gender effect should be further investigated. We suggest that the COPD decision aid be further tested in a community clinical setting.

**Cardiogenic Oscillations on the Airflow Signal during Continuous Positive Airway Pressure As a Marker of Central Apnea—**Ayappa I, Norman RG, Rapoport DM. *Chest* 1999 Sep;116(3):660–666.

Therapeutic decisions in patients with sleep apnea (eg, adjustment of continuous positive airway pressure [CPAP]) depend on differentiating central from obstructive apnea. Obstructive apnea is defined by cessation of airflow in the presence of continued respiratory effort, which is conventionally inferred from chest wall movement or intrathoracic pressure swings. Cardio-

# Tools of the Trade

Interested in the long-term oxygen therapy topics discussed in this issue? Here are some resources you may find helpful.

## Basic Oxygen Administration

Presents the primary goals of oxygen therapy and the clinical conditions that warrant oxygen administration. Also covers oxygen sampling techniques for various types of patients including newborns and various oxygen administration appliances. Includes oxygen administration hazards, assessment factors for evaluation of oxygen delivery, the principles of humidification and factors affecting efficiency of devices, proper attachment of oxygen devices, and trouble-shooting of bubble humidifiers. Software, 3 1/2" Disk. Requires Windows® 3.1 or higher.

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## Hemodynamics

Presents the basic concepts involved in monitoring and interpretation of hemodynamic values. It includes general guidelines for use and maintenance of lines, systemic blood pressure including central venous pressure, cardiac output, oxygen content, Swan-Ganz pulmonary artery catheter measurements, clinical applications of hemodynamic measurements, relationship between clinical conditions and hemodynamic measurements, and case studies which consist of 20 questions on clinical conditions, with associated laboratory and hemodynamic values. Software, 3 1/2" Disk. Requires Windows® 3.1 or higher.

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## Airway Management: Tricks of the Trade

Learn how to manage the obstructed airway and how to determine when an artificial airway is necessary. Also presented are the methods of assessing endotracheal tube positioning, monitoring the intubated patient, and determining when extubation is feasible. Featuring Charles G. Durbin, Jr., MD, FCCM, and David J. Pierson, MD. 80-minute videotape.

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## Hemodynamic Monitoring

Identifies the different forms of invasive and noninvasive hemodynamic monitoring, their main complications, and appropriate levels. Discusses how positive end-expiratory pressure and other therapies affect parameters. Featuring John J. Marini, MD, and David J. Pierson, MD. 80-minute videotape.

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## Blood Gas and Related Measurements:

### Laboratory Versus Bedside Devices

Presents the various means of obtaining blood gas information using invasive and noninvasive devices, the need for such devices, and when they should be used. Featuring Barry R. Shapiro, MD, and Richard D. Branson, BS, RRT. 80-minute videotape.

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## An Introduction to Hemodynamic Monitoring

Teaches you to recognize the types of equipment used for hemodynamic measurements. It also instructs in position of the pressure transducer, identification of pressure waveforms, and measurement of cardiac output. Discusses anatomic normal pressure values, oxygen saturation values, and the two major determinants of cardiac output. Individual Independent Study Package (IISP).

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## Tracheal Intubation I: Upper Airway Anatomy and Goals of Intubation

After completing this IISP, you will understand the rationale for tracheal intubation and be able to identify the important landmarks of upper airway anatomy. Individual Independent Study Package (IISP).

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## Tracheal Intubation II: Routes of Intubation

Describes the four routes of tracheal intubation and some advantages and hazards of each. Also presents the process for selecting the most suitable route in a given situation. Individual Independent Study Package (IISP).

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## Arterial Blood Gas Interpretation

Teaches ABG interpretation for administering therapy in a knowledgeable manner. Describes a systematic method that allows you to correctly classify the acid-base dysfunction and to relate the diagnosis concisely and coherently. Individual Independent Study Package (IISP).

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## Eight Hot Topics

### Program #1

#### **Pulmonary Rehabilitation: What You Need to Know**

*Live Videoconference - March 7, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - April 4, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: Julien M. Roy, BA, RRT, FAACVPR, and Richard D. Branson, BA, RRT*

What constitutes a sound pulmonary rehabilitation program? How do you go about setting up a rehab program? What's the role of assessment in developing an exercise prescription for the rehab of your patients? What are the issues surrounding reimbursement and what does the future hold? Learn the answers to these questions and gain an appreciation for the importance of pulmonary rehabilitation to your facility and your patients.

### Program #3

#### **Drugs, Medications, and Delivery Devices of Importance in Respiratory Care**

*Live Videoconference - April 25, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - May 16, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: James B. Fink, MS, RRT, FAARC and David J. Pierson, MD, FAARC*

Aerosol therapy is delivered to nearly 80% of respiratory patients. There are a number of new medications in development for both local and systemic administration to those patients. Which device to use, how to negotiate care plans, and how to educate both patients and caregivers are all topics that will be discussed. Perhaps of critical importance is getting the most medication delivered to the patient's lungs, which leads to a discussion of selecting the correct delivery device.

### Program #5

#### **Pediatric Ventilation: Kids Are Different**

*Live Videoconference - July 25, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - August 15, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: Mark Heullitt, MD, FAAP, FCCP and Richard D. Branson, BA, RRT*

There are significant differences in the anatomy and physiology of the respiratory systems between adults and children, posing problems for the practitioner attempting to mechanically ventilate a pediatric patient. Once the process is underway, the capabilities of the available mechanical ventilators and how they affect children pose additional problems. Children are so different, you need to stop and reassess actions you would normally take with an adult patient.

### Program #7

#### **Managing Asthma: An Update**

*Live Videoconference - September 19, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - October 17, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: Patti Joyner, RRT, CCM and Mari Jones, MSN, RN, FNP, RRT*

Asthma management is a hot topic for discussion. Everyone wants to implement a program at his or her facility. What will make a program work, and how do you know if it's successful? This program will provide you with the information you have been looking for in order to implement a program and determine how successful the program really is. You will be given guidance on how to analyze outcomes measures from a successful program.

### Program #2

#### **Pediatric Asthma in the ER**

*Live Videoconference - March 28, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - April 18, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: Timothy R. Meyers, BS, RRT and Thomas J. Kallstrom, RRT, FAARC*

The prevalence of pediatric asthma has increased dramatically in the last few years. The National Asthma Education and Prevention Program has provided guidelines for management of pediatric asthma. This program will discuss these issues as well as the role of care paths in the management of the disease. Additionally, there have been some significant advances in coping with pediatric asthma in the ER.

### Program #4

#### **Cost-Effective Respiratory Care: You've Got to Change**

*Live Videoconference - May 23, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - June 20, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: Kevin L. Shrake, MA, RRT, FACHE, FAAMA, FAARC and Sam P. Giordano, MBA, RRT, FAARC*

Practitioners frequently confuse the implementation of protocol treatment and case management. Both programs, if successfully implemented, can lead to cost savings. The problem most practitioners face is how to identify where costs are avoided and resources are conserved. Perhaps most critical is ensuring that the correct care is delivered at the proper time. The health care practitioner is key to the ultimate success of these programs.

### Program #6

#### **What Matters in Respiratory Monitoring: What Goes and What Stays**

*Live Videoconference - August 22, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - September 26, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: Dean R. Hess, PhD, RRT, FAARC and Richard D. Branson, BA, RRT*

The health care provider has an array of monitoring devices available in managing a patient. With all that technology available, which device is appropriate? What about those displays on ventilators? The availability of graphics during mechanical ventilation can provide a wealth of information. When is it essential? Under what circumstances should you pay close attention to those displays in the assessment of your patient?

### Program #8

#### **Routine Pulmonary Function Testing: Doing It Right**

*Live Videoconference - November 7, 11:30 a.m.-1:00 p.m. Central Time*

*Teleconference with Videotape - December 5, 11:30 a.m.-12:00 Noon Central Time*

*Presenters: Carl D. Mottram, BA, RRT, RPFT and David J. Pierson, MD, FAARC*

Pulmonary function testing at the bedside is being increasingly utilized as a diagnostic tool. Is it always appropriate? How can you assure competency of the person conducting the test? How can you assure quality assurance outside the pulmonary function laboratory? This program will provide you with the information you need to assure that this diagnostic test is properly conducted outside the laboratory.

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## Teleconference with Videotape Requirements

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## AARC Professor's Rounds

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genic oscillations in the airflow have been observed during some central apneas, but there is controversy over whether they correlate with airway patency. The present study investigates whether these oscillations are markers of the absence of respiratory effort (central apnea) without regard to airway patency. **METHODS:** We examined 648 apneas in 52 patients undergoing nocturnal polysomnograms and CPAP titrations. Airflow was measured using the output of the CPAP generator, and apneas were identified from reduction of airflow to  $< 10\%$  for  $> 10$  s. We used only the presence or complete absence of thoracoabdominal motion to classify apneas: obstructive apnea when motion was present (297 apneas); and central apnea if motion was totally absent (351 apneas). Central apneas most often occurred at sleep onset or followed arousal with a big breath. Using only the flow signal, all apneas were examined for the presence of cardiogenic oscillation by an observer blinded to other signals and apnea types. **RESULTS:** No obstructive apnea showed definite cardiogenic oscillations. In four cases, there was a suggestion of oscillation that was not regular enough to be called cardiac. Sixty percent of central apneas showed clear, regular oscillations at cardiac frequency. Cardiogenic oscillations also were seen intermittently during quiet exhalation in apnea-free periods. **CONCLUSION:** The presence of cardiogenic oscillations on the CPAP flow signal is a specific indicator of central apnea and may have a role in self-titrating CPAP algorithms. We speculate that transmission of these cardiac-induced oscillations may relate to the relaxation of thoracic muscles during central apnea and is impeded by high muscle tone during obstructive apnea.

**Efficacy and Compliance with Noninvasive Positive Pressure Ventilation in Patients with Chronic Respiratory Failure**—Criner GJ, Brennan K, Travaline JM, Kreimer D. *Chest* 1999 Sep;116(3):667–675.

**STUDY OBJECTIVES:** Previous studies have shown the acute effects of noninvasive positive pressure ventilation (NPPV) in chronic respiratory failure; however, information on the chronic effects of NPPV is limited. We examined the acute and chronic effects of NPPV on gas exchange, functional status, and respiratory mechanics in patients with chronic respiratory failure related to restrictive ventilatory disorders or COPD. **DESIGN:** Descriptive analysis of prospectively collected clinical data. **SETTING:** Inpatient noninvasive respiratory care unit and outpatient clinic of university hospital. **PATIENTS:** Forty patients with chronic respiratory failure (20 with severe COPD and 20 with restrictive ventilatory disorders). **INTERVENTIONS AND MEASUREMENTS:** All patients were admitted to a noninvasive respiratory care unit for  $20 \pm 3$  days for inpatient evaluation

consisting of medical treatment, rehabilitation, and NPPV evaluation and instruction. NPPV was titrated via a ventilatory support system (BiPAP; Respironics Inc; Monroeville, PA) or a portable volume ventilator (PLV 102; Lifecare, Inc; Boulder, CO) to achieve a  $\geq 20\%$  increase in baseline minute ventilation while monitoring gas exchange, expired volume, and clinical evidence of a decrease in the patient's work of breathing. **RESULTS:** The patients' mean age ( $\pm$  SD) was  $65 \pm 9.7$  years, and there was a 3:1 female:male predominance. In the noninvasive respiratory care unit, 36 patients used NPPV for  $7.31 \pm 0.26$  h/night. Four patients (three with COPD, one with restrictive disorder) withdrew from the study during the 3-week inpatient stay because they could not tolerate NPPV. Six patients (5 with COPD, 1 with restrictive disorder) used a portable volume ventilator and 34 patients used BiPAP (15 with COPD, 19 with restrictive disorders). At discharge, compared with at admission, daytime  $P_{aO_2}$ /fraction of inspired oxygen ( $F_{IO_2}$ ) increased ( $327 \pm 10$  vs  $283 \pm 13$  mm Hg;  $p = 0.01$ ),  $P_{aCO_2}$  was reduced ( $52 \pm 2$  vs  $67 \pm 3$  mm Hg;  $p = 0.0001$ ), and functional score increased ( $4.76 \pm 1.16$  vs  $2.7 \pm 1.64$  arbitrary units (AUs);  $p < 0.01$ ). Six months after discharge, improvements in  $P_{aO_2}/F_{IO_2}$  ( $317 \pm 10$  vs  $283 \pm 13$ ;  $p = 0.05$ ),  $P_{aCO_2}$  ( $52 \pm 2$  vs  $67 \pm 3$  mm Hg;  $p = 0.0001$ ), and functional score ( $5.66 \pm 0.41$  vs  $2.7 \pm 0.3$  AUs;  $p < 0.001$ ) were maintained compared with admission values. FVC, FEV<sub>1</sub>, and maximum inspired and expired mouth pressures were unchanged before and after long-term NPPV. Ten patients (7 with COPD, 3 with restrictive disorders) discontinued NPPV at 6 months, and 3 progressed to tracheostomy. The remaining 26 patients continued to use NPPV at the 6-month follow-up. They claimed to use NPPV for  $7.23 \pm 0.24$  h/night, but logged metered use was  $4.5 \pm 0.58$  h/night. Problems that required adjustment in either the mask (36%) or ventilator source (36%) included mask leaks (43%), skin irritation (22%), rhinitis (13%), aerophagia (13%), and discomfort from mask headgear (7%). **CONCLUSION:** NPPV acutely and chronically improves gas exchange and functional status in patients with chronic respiratory failure, but a significant number of patients do not tolerate NPPV on a chronic basis. Comprehensive follow-up is required to correct problems with NPPV and ensure optimal patient compliance.

**Atmospheric Pressure Changes and Outdoor Temperature Changes in Relation to Spontaneous Pneumothorax**—Smit HJ, Deville WL, Schramel FM, Schreurs JM, Sutedia TG, Postmus PE. *Chest* 1999 Sep;116(3):676–681.

**STUDY AIMS:** To examine the influence of atmospheric pressure (AP) and temperature changes on the incidence of idiopathic spontaneous pneumothorax (SP). **METHODS:** From

December 1991 through November 1993, 115 consecutive SP cases were selected. Patients were included after being in Amsterdam at least 1 full day before contracting the SP. Differences in air temperature and AP (provided hourly by the national weather bureau) for the days of the SP occurrence and the days previous to it were recorded to measure influences of air temperature and AP. The correlation between days with lightning and SP and clustering of SP was evaluated. **RESULTS:** SP occurred on 14.7% of the days in the 2-year period. There was no relationship between SP and a rise or fall in AP (Poisson regression). There was an average temperature rise of 0.57 degrees C from the day prior to the day of the SP, compared with a 0.08 degrees C fall on the days without SP. This difference is statistically significant and was consistent over the four seasons and both years. Seventy-three percent of the SP cases were clustered. A relationship between SP and thunderstorms was found. **CONCLUSIONS:** AP differences do not seem to influence the chance of developing SP. SP occurs in clusters, and more often 1 to 2 days after thunderstorms. Whether the identified temperature rise prior to the SP is a causative factor is unlikely; coexisting weather phenomena might explain this unexpected finding and should be studied in the future.

**Effect of Music on State Anxiety Scores in Patients Undergoing Fiberoptic Bronchoscopy**—Colt HG, Powers A, Shanks TG. *Chest* 1999 Sep;116(3):819–824.

**OBJECTIVE:** To study the effect of music on state anxiety levels in patients undergoing flexible fiberoptic bronchoscopy (FFB). **DESIGN:** Randomized clinical trial using pretests, posttests, and two groups. **SETTING:** Pulmonary special-procedures unit of a tertiary-care referral center. **PATIENTS:** Sixty adult patients: 30 patients received music during bronchoscopy and 30 control subjects received no music. **RESULTS:** The study population had baseline state anxiety levels similar to those previously reported in surgical patients ( $42.6 \pm 13$  vs  $42.7 \pm 14$ ;  $p$  value, not significant [NS]) and higher than those reported in normal working adults ( $42.6 \pm 13$  vs  $34.4 \pm 10$ ;  $p < 0.001$ ). Experimental and control groups were similar in patient and procedure-related characteristics and baseline pre-FFB state and trait anxiety scores. Although trait anxiety scores decreased significantly after the procedure (pooled post-FFB scores of  $32.6 \pm 10$  vs pre-FFB scores of  $35.5 \pm 11$ ;  $p < 0.001$ ), no reductions were noted in state anxiety (pooled post-FFB scores of  $42.8 \pm 13$  vs pre-FFB scores of  $42.6 \pm 13$ ;  $p$  value, NS). More importantly, playing music through headphones during FFB did not result in a statistically or clinically significant reduction in either state or trait anxiety when compared to control subjects. **CONCLUSION:** Relaxation music administered through headphones to pa-

tients during flexible bronchoscopy does not decrease procedure-related state anxiety.

**Salmeterol Does Not Compromise the Bronchodilator Response to Albuterol during Acute Episodes of Asthma**—Korosec M, Novak RD, Myers E, Skowronski M, McFadden ER Jr. *Am J Med* 1999 Sep;107(3):209–213.

**PURPOSE:** The present study was undertaken to determine whether regular use of salmeterol reduces the emergency effectiveness of albuterol. **PATIENTS AND METHODS:** Acutely ill asthmatic patients chronically taking salmeterol, and similar patients who were not taking salmeterol, were treated with albuterol, either as three aerosols of 2.5 mg every 20 minutes for 1 hour or two doses of 5.0 mg every 20 minutes. Peak expiratory flow measurements were monitored before and after each treatment. The time to disposition and the number of return visits were also recorded. **RESULTS:** One hundred fourteen patients, 57 who took salmeterol and 57 who served as control patients, completed the study. Thirty-three patients in each group received the lower dose of albuterol, and 24 were given the larger amount. There were no significant pretreatment differences between the salmeterol and control groups in the severity of symptoms or the degree of airway obstruction. Both albuterol regimens improved peak flow. Responses in the control group and in the salmeterol group were similar (low-dose albuterol increase in peak flow = 49%, control = 35%,  $P = 0.37$ ; high-dose albuterol increment in peak flow = 43%, control = 41%,  $P = 0.81$ ). There were no significant differences between the control group and the salmeterol group in the mean length of stay, the proportion of subjects admitted to the hospital, or the number of return visits. **CONCLUSIONS:** In patients with asthma, chronic use of salmeterol does not interfere with the effects of standard doses of albuterol for the treatment of acute decompensations.

**Analysis of Observer Variability in Measurement of Pulmonary Artery Occlusion Pressures**—Al-Kharrat T, Zarich S, Amoateng-Adjepong Y, Manthous CA. *Am J Respir Crit Care Med* 1999 Aug;160(2):415–420.

The goal of this study was to determine inter- and intraobserver variability in measurement of pulmonary artery occlusion pressure (P), comparing values recorded by critical care nurses and those measured by physician specialists. Critical care nurses (CCNs) obtained contiguous pulmonary artery and occlusion pressure paper tracings, up to twice a day, between June 1997 and March 1998. All tracings were interpreted on two separate occasions, in blinded fashion, by our Chiefs of Critical Care (CCMD) and Cardiology (CARD). Their values of P were compared with those that had been recorded by CCNs. One hundred and forty-seven measure-

ments of P were performed on 40 patients with a mean age of  $62.5 \pm 2.2$  yr and a mean APACHE II score of  $21.5 \pm 0.8$ . Either or both physician readers found 34 tracings as not satisfactory for P interpretation. Intraobserver agreement of P measurements, determined by correlation coefficients, was 0.91 for the CCMD and 0.87 for the CARD. Correlation coefficients for interobserver comparisons were 0.83 for CCMD-CARD, 0.66 for CARD-CCN, and 0.67 for CCMD-CCN. Clinically significant differences were observed between CCMD-CARD (range of differences, -11 to 12 mm Hg), CARD-CCN (-13 to 15 mm Hg), and CCMD-CCN (-11 to 15 mm Hg). When P readings were categorized as low (< 5 mm Hg), normal (5–15 mm Hg), and high (> 15 mm Hg), kappa values were 0.57 for CARD-CCMD, 0.51 for CARD-CCN, and 0.41 for CCMD-CCN comparisons. Interobserver variability was not explained by positive pressure ventilation or by the presence of (> 4 mm Hg) ventricular waves. The absolute values of interobserver differences in tracings with respiratory phasic variations (RPV)  $\geq 8$  mm Hg were significantly greater than for tracings with variations < 8 mm Hg ( $p < 0.05$ , except CCMD-CCN,  $p = 0.10$ ). Intraobserver differences also tended to be higher for tracings with RPV  $\geq 8$  mm Hg ( $p = 0.06$  and  $0.05$ ). When selected tracings were presented to 23 CCNs and 18 physicians, vari-

ability of P interpretation was twice as great for tracings with large RPVs as compared with those with minimal RPVs. These data suggest that observer variability of P interpretation is of potential clinical importance and that the degree of variability is associated with the magnitude of respiratory phasic variation of intrathoracic pressures. Although this could represent a local aberration, this study highlights a factor (respiratory phasic variation of P) responsible for significantly increased intra- and interobserver variabilities.

**Inhaled Nitric Oxide and Vasoconstrictors in Acute Respiratory Distress Syndrome**—Papazian L, Roch A, Bregeon F, Thirion X, Gaillat F, Saux P, Fulachier V, Jammes Y, Aufferay JP. *Am J Respir Crit Care Med* 1999 Aug; 160(2):473–479.

It has been suggested that the increase in  $PO_2$  observed with nitric oxide (NO) should be enhanced by the addition of a vasoconstrictor agent. The vasoconstrictor used in combination with NO should mimic or enhance hypoxic vasoconstriction. The aim of this study was to evaluate the respiratory and hemodynamic effects of norepinephrine (a nonspecific vasoconstrictor), almitrine bismesylate (a specific pulmonary vasoconstrictor), and inhaled NO, alone or together. During a 6-mo period, 16 patients

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presenting with ARDS were prospectively investigated. On inclusion, no patient was receiving cardioactive drugs. The protocol consisted of seven consecutive phases: baseline, norepinephrine (in order to obtain a 3 mm Hg rise in mean pulmonary arterial pressure [ $P_{pa}$ ]), almitrine bismesylate (16 micrograms/kg/min), inhaled NO (20 ppm delivered during inspiration), norepinephrine + inhaled NO, almitrine bismesylate + inhaled NO, almitrine bismesylate + norepinephrine + inhaled NO. General factorial analysis of variance showed that inhaled NO and almitrine bismesylate increased oxygenation ( $p < 0.0001$ ). Norepinephrine had no effect on oxygenation. A synergistic effect between inhaled NO and almitrine bismesylate was found ( $p < 0.05$ ), whereas norepinephrine did not affect the response to inhaled NO. Nitric oxide produced a significant decrease in  $P_{pa}$  and pulmonary vascular resistances (PVRI) ( $p < 0.0001$ ). Both almitrine bismesylate and norepinephrine induced an increase in  $P_{pa}$  ( $p < 0.0001$ ). Norepinephrine increased PVRI ( $p < 0.002$ ), whereas almitrine bismesylate had no effect on PVRI. The present results support the hypothesis that a selective pulmonary vasoconstrictor enhances the increase in oxygenation induced by inhaled NO, whereas norepinephrine attenuates this effect.

**Automatic Control of Pressure Support Mechanical Ventilation Using Fuzzy Logic**—Nemoto T, Hatzakis GE, Thorpe CW, Olivenstein R, Dial S, Bates JH. *Am J Respir Crit Care Med* 1999 Aug;160(2):550–556.

There is currently no universally accepted approach to weaning patients from mechanical ventilation, but there is clearly a feeling within the medical community that it may be possible to formulate the weaning process algorithmically in some manner. Fuzzy logic seems suited this task because of the way it so naturally represents the subjective human notions employed in much of medical decision-making. The purpose of the present study was to develop a fuzzy logic algorithm for controlling pressure support ventilation in patients in the intensive care unit, utilizing measurements of heart rate, tidal volume, breathing frequency, and arterial oxygen saturation. In this report we describe the fuzzy logic algorithm, and demonstrate its use retrospectively in 13 patients with severe chronic obstructive pulmonary disease, by comparing the decisions made by the algorithm with what actually transpired. The fuzzy logic recommendations agreed with the status quo to within 2 cm  $H_2O$  an average of 76% of the time, and to within 4 cm  $H_2O$  an average of 88% of the time (although in most of these instances no medical decisions were taken as to whether or not to change the level of ventilatory support). We also compared the predictions of our algorithm with those cases in which changes in pressure support level were actually made by an attend-

ing physician, and found that the physicians tended to reduce the support level somewhat more aggressively than the algorithm did. We conclude that our fuzzy algorithm has the potential to control the level of pressure support ventilation from ongoing measurements of a patient's vital signs.

**Positive End-Expiratory Pressure Preserves Surfactant Function in Preterm Lambs**—Michna J, Jobe AH, Ikegami M. *Am J Respir Crit Care Med* 1999 Aug;160(2):634–639.

Ventilation style influences lung injury and the amount of large-aggregate biophysically active surfactant in adult lungs. We asked how positive end-expiratory pressures (PEEP) would influence clinical responses and surfactant pools in surfactant-treated preterm lambs ventilated for 7 h with tidal volumes ( $V_T$ ) of 10 mL/kg. The 126-d gestation preterms were delivered and treated with 100 mg/kg recombinant human surfactant protein C (rSP-C) containing surfactant and ventilated with zero, 4, or 7 cm  $H_2O$  of PEEP. A comparison group was treated with natural sheep surfactant and ventilated with zero PEEP. Physiologic measurements were similar for lambs treated with rSP-C surfactant and natural surfactant. PEEP 4 and 7 improved oxygenation and compliance relative to either group of lambs ventilated with PEEP zero. The maximal lung volumes measured at 40 cm  $H_2O$  pressure after 7 h ventilation for the PEEP 4 and 7 groups were more than double those measured for either PEEP zero group. Alveolar surfactant pools were larger for the PEEP 7 group, and the large-aggregate fraction was increased for the PEEP 4 and 7 groups, resulting in large-aggregate pool sizes that were 3-fold higher for the PEEP 4 and 4-fold higher for the PEEP 7 groups relative to the PEEP zero group treated with rSP-C surfactant. All large-aggregate surfactants lowered minimal surface tensions of a captive bubble to less than 5 mN/m. In preterm surfactant-treated lambs PEEP improved lung function and maintained more of an rSP-C surfactant in the biophysically active form.

**Exacerbations of Asthma: A Descriptive Study of 425 Severe Exacerbations. The FACET International Study Group**—Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, et al. *Am J Respir Crit Care Med* 1999 Aug;160(2):594–599.

The identification, prevention, and prompt treatment of exacerbations are major objectives of asthma management. We looked at change in PEF, symptoms, and use of rescue beta-agonists during the 425 severe exacerbations that occurred during a 12-mo parallel group study (FACET) in which low and high doses of budesonide with and without formoterol were compared in patients with asthma. Oral corticosteroids were prescribed for severe exacerbations,

the main study end point, defined as the need for a course of oral corticosteroids ( $n = 311$ ) or a reduction in morning PEF of  $> 30\%$  on two consecutive days. PEF, symptoms, and bronchodilator use over the 14 d before and after the exacerbation were obtained from diary cards. Exacerbations were characterized by a gradual fall in PEF over several days, followed by more rapid changes over 2 to 3 d; an increase in symptoms and rescue beta-agonist use occurred in parallel, and both the severity and time course of the changes were similar in all treatment groups. Exacerbations identified by the need for oral corticosteroids were associated with more symptoms and smaller changes in PEF than those identified on the basis of PEF criteria. Female sex was the main patient characteristic associated with an increased risk of having a severe exacerbation. Exacerbations may be characterized predominantly by change in symptoms or change in PEF, but the pattern was not affected by the dose of inhaled corticosteroid or by whether the patient was taking formoterol.

**Cycle Ergometer and Inspiratory Muscle Training in Chronic Obstructive Pulmonary Disease**—Larson JL, Covey MK, Wirtz SE, Berry JK, Alex CG, Langbein WE, Edwards L. *Am J Respir Crit Care Med* 1999 Aug;160(2):500–507.

In patients with chronic obstructive pulmonary disease (COPD) the intensity of aerobic training is limited by dyspnea. Improving strength of the inspiratory muscles could enhance aerobic exercise training by reducing exercise-related dyspnea. We examined effects of home-based inspiratory muscle training (IMT) and cycle ergometry training (CET) in 53 patients with moderate to severe COPD ( $FEV_1$  % pred,  $50 \pm 17$  [mean  $\pm$  SD]). Patients were randomly assigned to 4 mo of training in one of four groups: IMT, CET, CET + IMT, or health education (ED). Patients were encouraged to train to the limits of their dyspnea. Inspiratory muscle strength and endurance increased in IMT and CET + IMT groups compared with CET and ED groups ( $p < 0.01$ ). Peak oxygen uptake increased and heart rate, minute ventilation, dyspnea, and leg fatigue decreased at submaximal work rates in the CET and CET + IMT groups compared with the IMT and ED groups ( $p < 0.01$ ). There were no differences between the CET and CET + IMT groups. Home-based CET produced a physiological training effect and reduced exercise-related symptoms while IMT increased respiratory muscle strength and endurance. The combination of CET and IMT did not produce additional benefits in exercise performance and exercise-related symptoms. This is the first study to demonstrate a physiological training effect with home-based exercise training.

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# Long-Term Oxygen Therapy

PART I OF  
TWO SPECIAL ISSUES

Containing the manuscripts and discussions  
from the State-of-the-Art Conference held  
August 6-8, 1999, in Cancún, Mexico.

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Conference faculty members—front row, from left: Jadwiga A Wedzicha MD, Robert M Kacmarek PhD RRT FAARC, David J Pierson MD FAARC, Thomas L Petty MD FAARC, Walter J O'Donohue Jr MD, Joshua O Benditt MD. Back row, from left: Dean R Hess PhD RRT FAARC, Gerard J Criner MD, Jan Zielinski MD, Robert M McCoy RRT, James K Stoller MD, Neil R MacIntyre MD FAARC, Patrick J Dunne MEd RRT FAARC.

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## New Science and Technology in Long-Term Oxygen Therapy

Long-term oxygen therapy (LTOT) has emerged as one treatment that clearly increases the length and quality of life in patients with advanced stable chronic obstructive pulmonary disease and chronic hypoxemia. This statement is based upon a large body of science that began in the mid-1960s and became firmly established by two major controlled clinical trials, the Nocturnal Oxygen Therapy Trial and the British Medical Research Council controlled clinical trial of LTOT. A summary of the state of the art of oxygen therapy was published in *RESPIRATORY CARE* in 1983 (*Respir Care* 1983;28[7]:857-930). In the intervening years, oxygen has been prescribed to millions in the United States, which is a major LTOT market, partially because of population size. The other reason why oxygen is prescribed more commonly per capita in this country than elsewhere probably relates to a longer duration of experience in LTOT.

LTOT was introduced in Europe in the late 1970s, and in Japan in the early 1980s. But many areas of the world, including Central and South America, Africa, and Asia have limited or no oxygen services. LTOT technology covers a range from compressed gas cylinders used alone to truly ambulatory liquid oxygen systems, which are most

commonly used in the United States and Europe. A concentrator, with or without provision for at least a portable high-pressure cylinder on wheels, is the most common oxygen technology used today.

The purpose of the present conference was to give an update from a scientific basis for LTOT, including its risks, and to consider how various technologies for oxygen administration can be most efficiently provided to those who need it. How truly ambulatory oxygen may improve tissue oxygen transport better than systems that limit activities of daily living, needs further study. This question was thoroughly discussed at this year's Conference, held in Cancún, Mexico, August 5th through August 8th, 1999. Articles in this and the February issue of *RESPIRATORY CARE* offer a complete review of where we stand in the knowledge and technology of oxygen for patients in need, and where we might be headed in the future.

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## Historical Highlights of Long-Term Oxygen Therapy

Thomas L Petty MD FAARC

### Introduction

Effect of Oxygen in Improving Hemodynamics, Reducing Red Cell Mass,  
and Increasing Exercise Tolerance

The Sugarloaf Conference

Two Major Randomized Clinical Trials

The British Medical Research Council Clinical Trial

The Nocturnal Oxygen Therapy Trial

Other Benefits from Oxygen

The Evolution of Home Oxygen Systems

Future Directions

Summary

[Respir Care 2000;45(1):29–36] *Key words: long-term oxygen therapy, chronic obstructive pulmonary disease, liquid oxygen, oxygen concentrator, ambulatory oxygen.*

### Introduction

The rich history of the development of long-term oxygen therapy (LTOT) began with Priestley's discovery of oxygen. The early pioneers, Barach, Cotes, and Gilson, and studies of ambulatory oxygen by groups in Denver, Colorado, and Birmingham, England, followed by the British Medical Research Council (MRC) clinical trial and the Nocturnal Oxygen Therapy Trial (NOTT) are herein reviewed. The introduction of home oxygen systems and future directions of LTOT are briefly considered.

History records that oxygen was first discovered by Joseph Priestley on August 1, 1774, when he obtained a colorless gas by heating red mercuric oxide. He recognized that the candle flame would burn brighter in what he had termed "dephlogisticated air." He captured the gas in an inverted bell, and he and two mice were the first to breathe this "pure air." He noted a "light and easy feeling" and remarked, "who can tell but that in time this pure air

may become a fashionable article in luxury."<sup>1,2</sup> Carl Wilhelm Scheele, a Swedish chemist, also discovered oxygen, maybe as early as 1773.<sup>3</sup> Priestley's friend Antoine Lavoisier successfully repeated Priestley's original experiment and named the newly discovered gas oxygen. Oxygen was first used in dental anesthesia as early as 1868.

The first recorded use of oxygen in acute bacterial pneumonia was in York, Pennsylvania, on March 6, 1885. Dr George Holtzapple produced oxygen from chlorate of potassium and black oxide of manganese by heating the chemicals in a large glass cylinder with a flame from a lamp. The resultant oxygen was delivered to a young man's face via rubber tubing. After several hours the crisis passed and the young man recovered.<sup>4</sup> The nasal catheter came to be used at around the turn of the century. Other oxygen delivery devices were soon to follow.

Following John S Haldane's expedition to Pike's Peak in 1913, he concluded in his landmark article in the *British Medical Journal* in 1919 that "partial anoxia means not a mere slowing down of life, but progressive, and perhaps irreparable damage to human structure".<sup>5</sup> Haldane predicted that oxygen would soon be used in hospitals.

Alvan Barach was the first to systematically employ oxygen for the treatment of bacterial pneumonia.<sup>5</sup> Barach modified an oxygen tent, originally invented by Leonard Hill.<sup>6,7</sup> Barach was also interested in the role of oxygen and relief of dyspnea during exercise. In 1958 he devel-

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oped a small transfillable oxygen cylinder suitable for use during exercise. Cotes and Gilson also gave oxygen to ambulatory patients from small portable high-pressure cylinders in the United Kingdom (UK). Cotes reported on increased walking time and improved arterial oxygen saturation.<sup>8</sup> By 1955 approximately 30% of all "chemists" in Wales and Monmouthshire (population 2.6 million) were supplying oxygen by prescription to an, at that time, astonishing 860 patients. Oxygen cylinders were the only modality of therapy in that era. An expanded discussion on oxygen and exercise will be presented in an article on ambulatory oxygen therapy in the next issue of *RESPIRATORY CARE*.

### Effect of Oxygen in Improving Hemodynamics, Reducing Red Cell Mass, and Increasing Exercise Tolerance

The first liquid transfillable systems became available from the Linde Corporation in 1965. The Denver Group enrolled 6 patients on the basis of clinical evidence of severe pulmonary hypertension, erythrocytosis, hematocrit  $> 55\%$ , and markedly reduced exercise tolerance.<sup>9</sup> These 6 patients were admitted to a clinical research unit for the purpose of stabilization for one month, during which no oxygen was used. During stabilization, administration of bronchodilators, diuretics, and cardiac glycosides when indicated, and treatment of any evidence of infection provided for clinical stabilization. Patients were encouraged to eat a high-calorie diet and exercised systematically each day to improve physical conditioning and to increase exercise capability. At the end of a control month, cardiac catheterization was done to measure pulmonary pressure, cardiac output, and pulmonary vascular resistance. Chromium-51-tagged red cell mass determinations were also made.<sup>9</sup> During the second month, the patients were maintained on the same diet and maintenance medications, and oxygen was administered by nasal canula at a flow sufficient to bring oxygen saturation above 90% during rest and exercise. In all patients, this required 1–3 L/min, averaging 2 L. At the end of one month, cardiac catheterization and red cell mass studies were repeated. Marked reductions in pulmonary artery pressure and pulmonary vascular resistance were observed in 4 of the 6 patients. The red cell mass improved in 4 of the 5 patients in which both determinations could be accomplished. The most dramatic outcome was the markedly increased exercise tolerance in these patients (Fig. 1).

The first of these oxygen study patients became our first home care patient. Pictures of his quality of life and home functioning have been reported on numerous occasions (Figs. 2 through 6). It is obvious, even from these pictures, that a marked transformation in this patient's general ap-

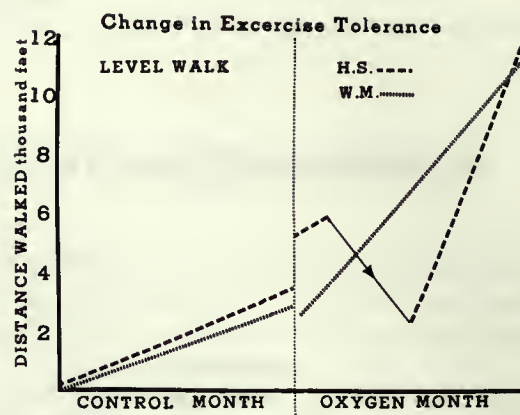


Fig. 1. Improvement in exercise tolerance in two patients trained at level walk. Note slow change during control month, and marked rapid rise in tolerance during oxygen month. W.M. and H.S. are the patients' initials. Temporary decrease in H.S.'s exercise tolerance during the oxygen month was due to an episode of acute bronchitis. (From Reference 9.)



Fig. 2. The first ambulatory oxygen patient in the Denver study. The bandage is over a stitch abscess at an old tracheostomy site. (From Reference 2.)

pearance and global function was achieved by the use of portable LTOT.

At approximately the same time, an almost identical study was done in Birmingham, England, which resulted in exactly the same conclusions about hemodynamic improvements and red cell mass.<sup>10</sup> Formal exercise studies were not conducted by the Birmingham group, largely because high-pressure cylinders were used. However, these



Fig. 3. Same patient as in Figure 2 carrying oxygen while coming to clinic one year later.

were used with a "trolley," so some degree of ambulation was possible while pushing the oxygen cylinders. Although no accounts of exercise tolerance are reported, the authors remark, "Exercise tolerance increased remarkably . . . even though there was no specific program of training."

In 1968 we reported on 20 patients with advanced chronic obstructive pulmonary disease (COPD) who received continuous ambulatory oxygen therapy from a liquid oxygen portable system for longer periods of time.<sup>11</sup> In that article we showed crude anecdotal evidence of improvement in cor pulmonale, with evidence of improvement in electrocardiograph changes and in the cardiac silhouette, with resolution in right ventricular size as a result of 6 months of oxygen administration. This report also documented a progressive reduction in hematocrit and an increase in dry body weight over one year, which suggested some nutritional or metabolic benefit from LTOT. In this paper, we demonstrated a reduction in hospitalizations in one dramatic illustration showing the size of a patient's hospital record before and after oxygen, during an equal 18-month period (Fig. 7).<sup>11</sup>



Fig. 4. Patient transfilling oxygen system used in the home. (From Petty TL, Ambulatory and home care. In: Petty TL, editor. Intensive and rehabilitative respiratory care. Philadelphia: Lea & Febiger, 1971, pp 301-331.)

Following these original observations, other investigators in the UK focused on the daily requirements of oxygen to reverse pulmonary hypertension in patients with COPD.<sup>12,13</sup> These studies gave evidence that oxygen delivered from a stationary source for as little as 15 hours per day resulted in the improvement of pulmonary hypertension in some, but not all, patients. There was even a suggestion that 12 hours of oxygen could be effective.<sup>12,13</sup>

In a later report, the Denver Group was able to show an improvement in survival in patients before and following oxygen administration with clinical evidence of cor pulmonale, compared with historical controls from the Veterans Administration-Armed Forces study on course and prognosis in COPD.<sup>14</sup> A similar survival benefit was not found in patients who did not have clinical evidence of cor pulmonale.<sup>14</sup> It must be emphasized that all of these early studies were in small groups of patients without a contemporary cohort comparison group.

### The Sugarloaf Conference

In the early 1970s the National Heart, Lung & Blood Institute organized a major conference to evaluate the scientific basis of outpatient respiratory care practices.<sup>15</sup> This landmark conference was held in Sugarloaf, Pennsylvania, in May 1974 and spawned the Nocturnal Oxygen Therapy Trial (NOTT)<sup>16</sup> and the Intermittent Positive Pressure Breathing (IPPB) trial.<sup>17</sup>



Fig. 5. Patient doing household tasks, including caring for his invalid wife.



Fig. 6. Patient enjoying gardening outside of the home. (From Reference 11.)

## Two Major Randomized Clinical Trials

### The British Medical Research Council Clinical Trial

Our colleagues in the UK, led by the late David Flenley, asked an important question about the treatment of patients with COPD and chronic stable hypoxemia (arterial oxygen tension  $[P_{aO_2}] \leq 55$  mm Hg) and the effect of LTOT on survival. In a multicenter trial in the UK, the patients were randomized to receive either 15 hours (including the hours of sleep) of oxygen from a stationary system or no oxygen.<sup>18</sup> Figure 8 shows a survival curve from this study. It is interesting that improvement in survival does not appear until after 500 days.

### The Nocturnal Oxygen Therapy Trial

The NOTT enrolled 203 patients in 6 centers. The requirements for entry included  $P_{aO_2} \leq 55$  mm Hg in the 3-week stabilization period, during which bronchodilators and antimicrobials were used, as indicated. Patients were exercised on a daily basis to improve physical condition-

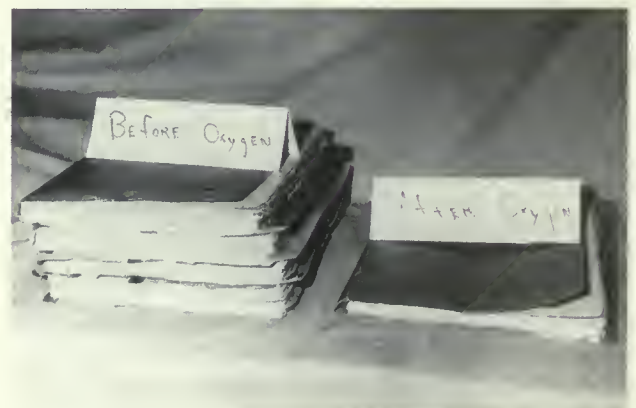


Fig. 7. Size of a patient's hospital record before and after oxygen, during an equal 18-month period. (From Reference 11.)

ing during the stabilization period. At the end of this stabilization phase the oxygen tension in 45 subjects improved to the extent that they no longer qualified while breathing room air; the oxygen tension had improved to  $\geq 55$  mm Hg during the stabilization period.<sup>19</sup> A few patients with an oxygen tension of 55–59 mm Hg were also entered

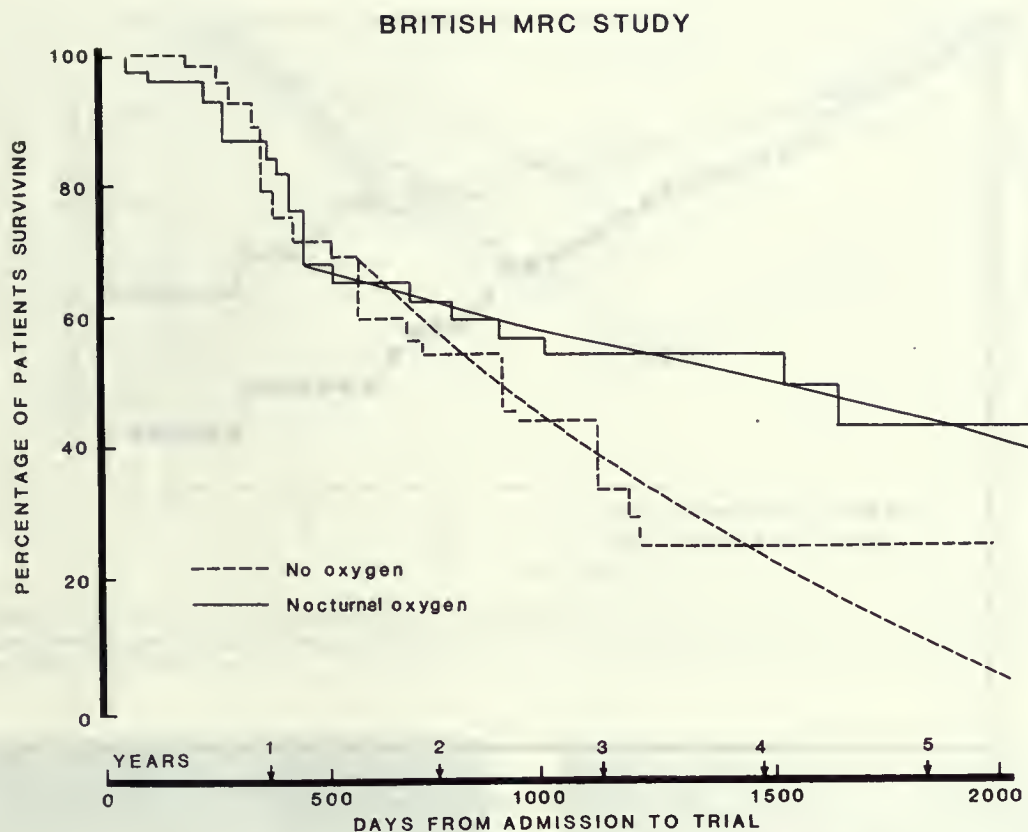


Fig. 8. Survival in the British Medical Research Council study comparing oxygen for 15 hours a day from a stationary source, compared with no oxygen. (From Reference 18, with permission.)

into the study because of clinical evidence of cor pulmonale based on electrocardiograph criteria and/or a hematocrit value of 55 or higher. In the NOTT only 4 patients were considered too ill to enter the stabilization period without oxygen.<sup>19</sup> Other exclusion criteria were the presence of serious comorbidity, refusal by the patient to follow a complex protocol that required two cardiac catheterizations, and residence too far from the testing center for the necessary close observations required by this study.<sup>19</sup>

Patients were randomized to receive either nocturnal oxygen therapy (NOT) using a stationary source or continuous oxygen therapy (COT). The randomization process resulted in patients who were excellently matched by age, sex, ethnic background, years of formal education, physiologic tests during both rest and exercise, pulmonary pressure, and pulmonary vascular resistance. The survival outcome is presented in Figure 9. Survival differences at 12, 24, and 36 months are statistically significant ( $p < 0.01$ ).

Since the demographics and disease severity of COPD patients in the MRC and the NOTT studies were quite similar, it is reasonable to compare the survival curves. This is done in Figure 10. In brief, this figure shows that survival in COPD with chronic stable hypoxemia is poor

when oxygen is not given. Survival is better in patients who received 12 or 15 hours of oxygen. Survival was best in patients who received nearly continuous oxygen from an ambulatory system. These differences in survival could have been related to the duration of oxygen therapy, the method, or both. The issues surrounding exercise and oxygen are presented in the companion article in the next issue of *RESPIRATORY CARE*.

#### Other Benefits from Oxygen

In earlier studies, Krop et al found improved brain function in patients with advanced COPD and the result of breathing oxygen compared with air.<sup>20</sup> Later, in the NOTT study, Grant et al found significant impairment in brain function prior to receiving oxygen in NOTT patients, compared with well-matched neighborhood controls.<sup>21</sup> Patients who received both NOT and COT had improved brain function at the 6-month observation point. But only COT patients had continued improvement in brain function at the end of one year, with a slight decline in the NOTT patients.<sup>21,22</sup>

Numerous studies of the quality of life were conducted in the NOTT. Although global benefit was obvious to most

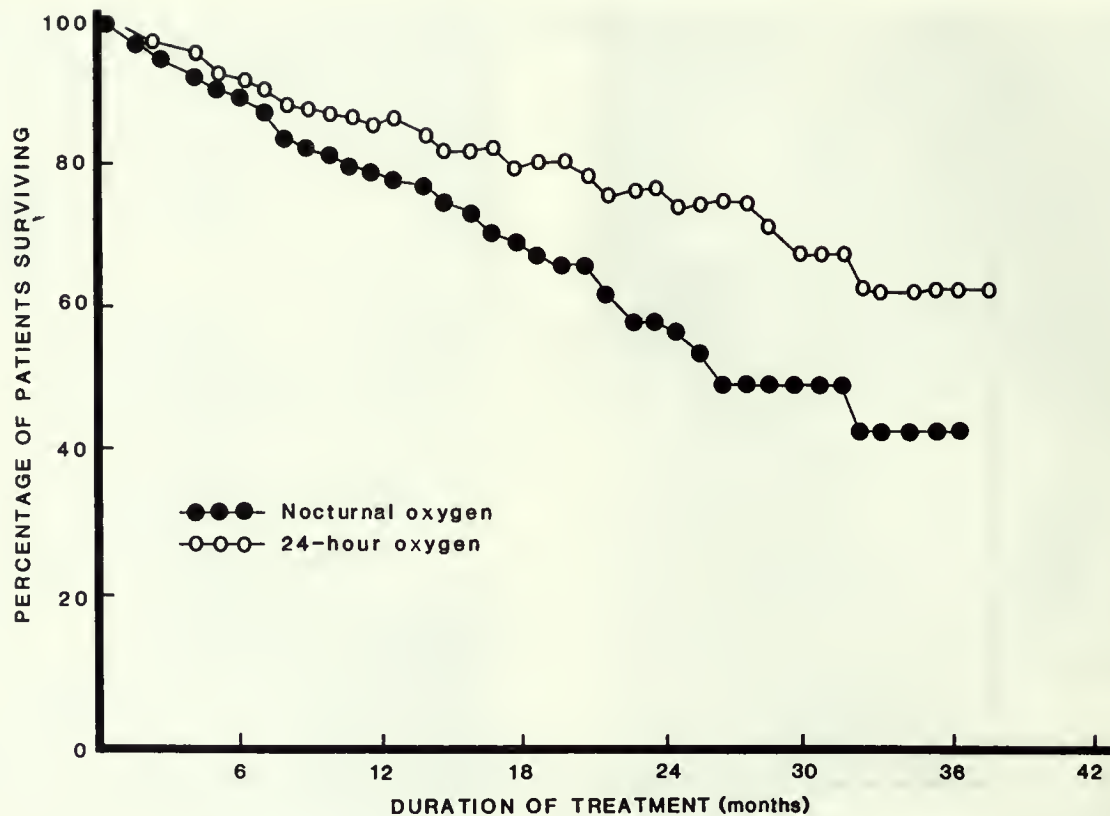


Fig. 9. Survival in the Nocturnal Oxygen Therapy Trial where "24-hour oxygen" duration was actually 19.4 hours median and 17.7 hours mean. Nocturnal oxygen by diary was for 11.8 hours mean from a stationary system. (From Reference 17, with permission.)

observers, actual quantification of the quality of life by specific instruments was somewhat difficult. The best estimates were derived from the numerous neuropsychologic studies, which have previously been reported.<sup>22</sup> These studies showed the profound effect of COPD and hypoxemia in various indices of brain function improvement and a small but significant improvement in brain function with the use of oxygen. It is difficult to separate the effects of oxygen from pulmonary rehabilitation (ie, exercise physical conditioning and nutritional repletion) in such studies.

### The Evolution of Home Oxygen Systems

The first home oxygen systems were high-pressure compressed gas cylinders similar to present large H or K cylinders. Some experiments in the transfilling from large high-pressure cylinders to small portable gas cylinders were attempted, but never became commercially available on a widespread basis (Fig. 11). The advent of liquid portable oxygen in the mid 1960s provided a revolution in home oxygen systems.<sup>23</sup> Transfilling liquid oxygen systems are the major truly ambulatory systems applied today.

The first oxygen concentrator was developed in the UK and used a calcium aluminum silicate (molecular sieve

absorptive principle).<sup>24</sup> In the early 1970s a membrane system was developed (Fig. 12). This membrane oxygen concentrator system was evaluated in 6 patients and was demonstrated to improve hypoxemia at a higher liter flow than was required from a concentrator using the molecular sieve principle in 12 patients.<sup>25</sup> It produced approximately 40% oxygen at a flow of 1–8 L/min.

Molecular sieve devices soon became the predominant concentrator system used in this country and elsewhere in the world. Today, the mostly commonly prescribed home oxygen system is a molecular sieve concentrator and an E cylinder as a back-up device for electrical power failure and to allow for a minimal degree of ambulation with oxygen outside of the home. Probably 80% of LTOT patients use this system today, even though it has significant limitations under conditions of full ambulation and full activities of daily living. See the companion article in the next issue of *RESPIRATORY CARE*.

Recently, three manufacturers have developed technologies for filling a small high-pressure cylinder from a concentrator. Whether or not these systems will be practical, durable, and economical remains to be determined. These small high-pressure cylinders are usually used with an inspiratory control device in order to conserve oxygen

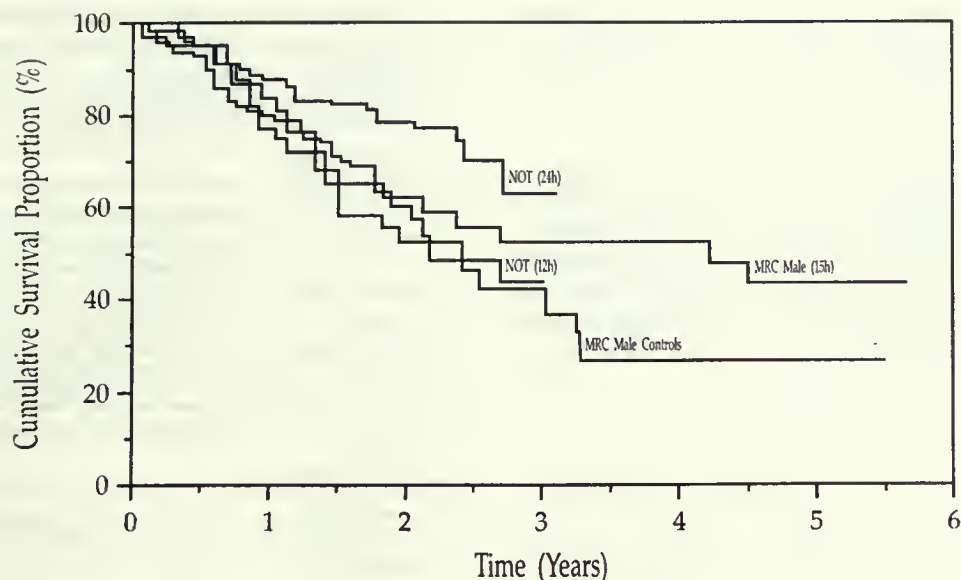


Fig. 10. Comparison of survival curves of Nocturnal Oxygen Therapy study (NOT) and British Medical Research Council study (MRC). (From Cooper CB. Long-term oxygen therapy. In Casaburi R, Petty TL, editors. Principles and practice of pulmonary rehabilitation. Philadelphia: WB Saunders, 1993, p 184, with permission.)



Fig. 11. A simple system of transfilling a small portable high-pressure system from a large K cylinder. (From Petty TL. Ambulatory and home care. In: Petty TL, editor. Intensive and rehabilitative respiratory care. Philadelphia: Lea & Febiger, 1971, pp 301-331.)

and thus to increase the hours of ambulatory oxygen available for ambulation outside of the home.

### Future Directions

A number of inventors have tried to develop a portable oxygen concentrator. One such device now exists that weighs slightly less than 10 pounds and uses membrane



Fig. 12. The first membrane oxygen system studied in Denver. The arterial blood gas sample has just been obtained.

technology to provide up to 1 L of 40% oxygen for only 1 hour. This is insufficient for practical usage. Practical portable concentrators should weigh no more than 10 pounds, produce 90% or more oxygen, and provide at least 2 L of oxygen for a minimum of 4 hours.

New technology exists that produces a significant amount of liquid oxygen by diversion of 1 L flow from a concentrator into a cryocooler device. Prototypes of such devices have been under evaluation for more than a year. Successful filling of conventional ambulatory liquid oxygen systems has been accomplished. Whether or not the techno-

logic details and widespread production of a home liquid oxygen generating system can be made practical remains to be seen.

### Summary

The story of the development of oxygen and its role in mitigating the ravages of chronic stable hypoxemia have been fascinating. Today, over one million Americans receive home oxygen each day, usually for COPD, from one of the three available systems. The future requires less expensive, highly portable, and practical devices for use during all activities of daily living.

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### Discussion

**Kacmarek:** I was quite intrigued about the system you mentioned, the one that takes a concentrator gas and liquefies it. How close is that to being commercially available? I must admit I was unaware that this technology was available.

**Petty:** Well, the timetable is to have it ready for the November MedTrade show in New Orleans. I don't know whether they'll meet that timetable or

not. There's some electronic problems and there's some engineering hurdles to jump through that may limit this. I have been there. The corporation is called IN-X. I've seen it work. It does make liquid oxygen, but whether it can be made practical soon enough, I don't know. There's another company in California working on similar technology. So the fact that the technology exists at all I think is great. And somebody is going to be able to do it. You know, once you put a man on the

moon, you can do it again. It's hard to discuss history because history is a fact. Facts are open to different interpretations, though. Please feel free.

**O'Donohue:** That was a wonderful presentation, Tom. You know, in thinking about the NOTT study, the fact that these patients were receiving oxygen for a little less than 19 hours daily may be critically important. A number of studies with transtracheal oxygen have shown improved physio

logic benefits through improved compliance, though no study has been able to look at survival. One of the studies that may add light was done by Selinger and associates and showed that in COPD patients who were on oxygen, if the oxygen was stopped for as much as 3 hours a day they developed increased pulmonary artery pressure.<sup>1</sup> The NOTT study patients were obviously off oxygen for more than 3 hours if they were using it for 19 hours. So, I think there may be adverse physiologic changes that occur when you're off oxygen for that much time each day.

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**Petty:** I think so too. Every cell in the body requires energy production, and of course as energy supply begins to dwindle, the body takes on priorities of where to put the energy. You know, it's a fact that no human can live above 18,000 feet for more than a few weeks, because you can't maintain your body weight above 18,000 feet. I believe that that's because your energy to the total body system begins to fail, and you start shutting down certain things like the skin and the gut. You can get to the top of Mount Everest on a good day with a  $P_{O_2}$  of about 28, but there's all kinds of enzymatic changes and maybe even some central nervous system changes in these people who put themselves through that experiment, so oxygen is at the end of the energy chain. I think that's key to the whole thing. I think that if we're to do well with our patients who have significant hypoxemia, we're going to have to correct it most or all of the time.

**Dunne:** Tom, are you aware of any technological developments in the area of oxygen concentrators themselves, such as moving away from the traditional pressure swing absorption-

compressor toward a different type of membrane technology to reduce the weight, power consumption, and perhaps even improving portability?

**Petty:** There are a number of small business grants that support projects that are aiming to produce oxygen from a small concentrator with membrane technology. Maybe Bob McCoy can tell us more about that, because he has some interest in this area too. Is there anything you can tell us about that?

**McCoy:** There's a company in Dublin, Ohio, called NetMed that has a ceramic concentrator that is supposedly smaller, lighter, and quieter than traditional sieve concentrators. This type of concentrator can produce close to 99% pure oxygen. Another company called CMT exhibited a membrane-type oxygen enricher at the MedTrade last year. The membrane-type concentrator produced about 30% oxygen. Neither of these companies has introduced their products in the United States market at this time, yet they are leading the way toward a move to a smaller, lighter type concentrator for mobility.

**Petty:** Priestley made his oxygen from mercuric oxide, and Holtzapple from manganese oxide, any kind of oxide like that could make oxygen out of solid-state material, although it's very expensive. We once had a demonstration of solid-state oxygen portable system. Once you start, you can't stop it. The trouble is you have to scrub the chlorine because you use perchlorate for part of the chemical reaction. But solid-state oxygen is used in some aircraft as the backup system for decompression. So, it's another possibility.

**Spratt:**\* You made a point there that we really need to focus more on getting people to use their oxygen 24

hours a day. I wonder if the question shouldn't be restated. Our goal is not necessarily just to use oxygen, but to produce normoxemia in these patients, and right now one of the things we deal with is  $O_2$  at 2 L/min is almost a universal order. The studies that have looked at this show that many people on 2 L/min still spend a significant percentage of the day below 90% arterial oxygen saturation measured by pulse oximetry.<sup>1-4</sup> This is a large number of patients. Shouldn't our focus be more on producing 24-hour normoxemia rather than 24 hour  $O_2$  usage? And, how do we address that?

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**Petty:** I think so, and with that in mind, Greg, during the NOTT study, and with some data, we added a liter during the hours of sleep and exercise, so you're right. Two L a minute was a starting point, but during sleep and exercise, they were on 3 L empirically. You know where 2 L of oxygen came from? I think it came from the Denver study where we did 17 people at 1 L, 3 L, and 5 L. And 1 L wasn't enough and 3 L was too much, so we said, well, 2 L then should be it. That was published about 1967.<sup>1</sup> At least that's how we got started on 2 L as the average liter flow.

\*Gregg Spratt, Rotech Medical Corporation, Kirksville, Missouri.

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**Wedzicha:** Tom, thank you for the excellent presentation. Can I ask you, as a non-American, about numbers of patients on oxygen therapy and what's being done about it in the United States? Can I give you an example? In the United Kingdom we have about 18,000 patients at the moment, but we've estimated that there are at least 40,000–50,000. Do you still have a similar problem in the United States, of under-diagnosis of chronic hypoxemia? If you haven't, what do you think specifically in the United States has enabled more patients to come forward? Is it interest of physicians, screening programs, or other factors?

**Petty:** Well it's a very important question you ask because percent-wise

per capita we have far more people on oxygen in the United States than any other country in the world. You might argue that it's too many people. It may well be, but I think it goes to over-prescribing, because we had this magic number  $P_{O_2}$  of 55 or less and you go on oxygen. I see an awful lot of people put on oxygen who don't need it physiologically. Matter of fact, if I'm going to use a  $P_{O_2}$  of 55, I could put everybody in the city of Leadville, Colorado, over 10,000 people, on oxygen immediately—they all qualify under our reimbursement plan. I've even threatened to put a clinic up there to justify oxygen, because everybody in that town has a  $P_{O_2}$  of 55 or less. Now, what goes on in Leadville? Well, there's a higher prevalence of pulmonary hypertension there than elsewhere in the world. The age-specific death rate from all kinds of diseases is higher in Leadville. There are very good data from the state health department. So if you're a normal person, you

can compensate for chronic stable hypoxemia.

Living on Mount Evans for a month, we could compensate in recovering our mentality scores. Because what happens when your  $P_{O_2}$  goes below 50 is you get neurotransmitter problems. Your cells don't die, but you have cell miscommunication. Then you come back and recover. Now some people with chronic stable hypoxemia should not be put on oxygen, even if they have the indications to go on oxygen, because they get depressed. Some people equate going on oxygen with imminent death. Everybody knows somebody who went on oxygen, and they died, you see. I have taken people off of oxygen saying "You were a lot better before your doctor put you on this oxygen. You were getting out and doing things." And I get rid of the oxygen. Some people do that on their own. There are 2 sides to the oxygen story. I think we probably over-prescribe, yet I think there are some areas that are underserved.

# Pathophysiology and Clinical Effects of Chronic Hypoxia

David J Pierson MD FAARC

## Introduction

### Mechanisms of Tissue Hypoxia

### Physiologic Responses to Hypoxia

#### Respiratory System

#### Cardiovascular System

#### Central Nervous System

#### Adaptation to Altitude

### Symptoms and Signs of Hypoxia

### Chronic Mountain Sickness

### Hypoxia during Sleep

### Chronic Hypoxia in Chronic Obstructive Pulmonary Disease

#### Pathogenesis of Cor Pulmonale in Chronic Obstructive Pulmonary Disease

#### Clinical Manifestations of Hypoxia and Cor Pulmonale in Chronic Obstructive Pulmonary Disease

#### Effects of Hypoxemia on Mortality in Chronic Obstructive Pulmonary Disease

## Summary

[Respir Care 2000;45(1):39–51] *Key words: hypoxia, hypoxemia, desaturation, respiratory system, clinical effects, altitude, chronic obstructive pulmonary disease, cor pulmonale, oxygen therapy, mortality.*

## Introduction

No aspects of respiratory care receive more attention in both education and clinical practice than assessing whether the body is getting enough oxygen and providing more oxygen when it is not. Several years ago a RESPIRATORY CARE Journal conference focused on problems with oxygenation in the critically ill patient.<sup>1</sup> For that conference I reviewed the pathophysiology and clinical effects of an acute deficiency of oxygen.<sup>2</sup> To lay the physiologic groundwork for this conference on long-term oxygen therapy (LTOT), this article addresses the pathophysiologic and

clinical effects of chronic oxygen deficiency in patients with pulmonary disease. After clarifying the terminology used to describe impaired oxygenation in the clinical setting, it discusses the basic physiologic mechanisms of tissue hypoxia, the effects of oxygen deficiency on the various organ systems of the body, and the clinical manifestations of chronic hypoxia in different contexts. Pertinent to the context of this conference, the last section focuses in some detail on the effects of chronic hypoxia in patients with chronic obstructive pulmonary disease (COPD).

Although clinicians use the terms hypoxia and hypoxemia every day, the majority of textbooks of physiology, respiratory care, and pulmonary medicine do not give explicit definitions for them. Dictionaries define them, but they vary somewhat in how they do this (Table 1).<sup>3–5</sup> Although the wording is a bit different, all three of the commonly used dictionaries in the table state that hypoxia is a decrease in tissue oxygen supply below normal levels. *Stedman's Medical Dictionary*<sup>5</sup> also lists several subtypes of hypoxia, which include the following terms relevant to this article:

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Table 1. Definitions of Hypoxia-Related Terms from Three Dictionaries

| Term      | Webster's <sup>3</sup>                                                    | Dorland's <sup>4</sup>                                                                                            | Stedman's <sup>5</sup>                                                                                                          |
|-----------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Hypoxia   | A deficiency in the amount of oxygen that reaches the tissues of the body | Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of tissue by blood     | Decrease below normal levels of oxygen in inspired gases, arterial blood, or tissue, short of anoxia                            |
| Anoxia    | An abnormally low amount of oxygen in the body tissues                    | A total lack of oxygen; often used interchangeably with hypoxia to mean a reduced supply of oxygen to the tissues | Absence or almost complete absence of oxygen from inspired gases, arterial blood, or tissues; to be differentiated from hypoxia |
| Hypoxemia | Inadequate oxygenation of the blood                                       | Deficient oxygenation of the blood; hypoxia                                                                       | Subnormal oxygen of arterial blood, short of anoxia                                                                             |

• Anemic hypoxia: hypoxia due to a decreased concentration of functional hemoglobin or a reduced number of red blood cells, as seen in anemia and hemorrhage;

• Hypoxic hypoxia: hypoxia resulting from a defective mechanism of oxygenation in the lungs, as caused by a low tension of oxygen, abnormal pulmonary function, airway obstruction, or a right-to-left shunt in the heart;

• Ischemic hypoxia: tissue hypoxia characterized by tissue oligemia and caused by arteriolar obstruction or vasoconstriction;

• Oxygen affinity hypoxia: hypoxia due to reduced ability of hemoglobin to release oxygen;

• Stagnant hypoxia: tissue hypoxia characterized by intravascular stasis due to impairment of venous outflow or decreased arterial inflow.

The definition of anoxia varies somewhat more than that of hypoxia in the sources commonly available to clinicians. The former term generally refers to a more severe state of oxygen deficiency and generally carries an implication of irreversible damage, as in anoxic encephalopathy following cardiac arrest. As shown in Table 1, the greatest variation of all in the context of this article is encountered in definitions for the term hypoxemia. In *Dorland's Illustrated Medical Dictionary*<sup>4</sup> hypoxemia is a synonym for hypoxia. However, all three sources say that hypoxemia refers to deficient oxygen in the blood. *Stedman's*,<sup>5</sup> but not the others, indicates that hypoxemia refers specifically to arterial blood.

None of the dictionaries cited, nor any of the textbooks I could find in preparing this article, define hypoxemia in the setting of the abnormal oxygenation we encounter clinically. That is, none of them say that it means "less oxygen than would be present in a normal person's blood under the same circumstances." For clinical purposes I will therefore use hypoxemia to mean a decreased oxygen tension ( $P_{O_2}$ ) in the blood below the normal range. Thus, the term should not be used when  $P_{O_2}$  is in the normal range, even if pulmonary gas exchange is markedly deranged or there is one of the other subtypes of hypoxia defined above.

Using this definition, a patient with an arterial  $P_{O_2}$  ( $P_{aO_2}$ ) of 100 mm Hg is not hypoxemic. This would be true even if to achieve that  $P_{aO_2}$  the patient had to breathe a high

fraction of inspired oxygen ( $F_{IO_2}$ ), or if the hemoglobin concentration (and thus the blood's total oxygen content) were greatly reduced. Finally, in the absence of consistency in the cited references, since a reduced  $P_{O_2}$  may be as important clinically in mixed venous blood as it is in the arterial blood, whether the blood in question is venous or arterial should be specified when referring to hypoxemia.

This article is ultimately about hypoxia at the tissue level. Directly measuring tissue oxygenation is not feasible in most clinical circumstances, however, and either  $P_{aO_2}$  or arterial oxyhemoglobin saturation ( $S_{aO_2}$ ) is usually measured. Nonetheless, it is important to remember that it is the adequacy of tissue oxygen supply, not necessarily the values of  $P_{aO_2}$  or  $S_{aO_2}$ , that determines whether the patient's life or organ function is threatened.

### Mechanisms of Tissue Hypoxia

Figure 1<sup>6</sup> emphasizes the interconnectedness of the components of tissue oxygenation. Oxygen enters the body via the lungs, is transported to the tissues via the blood, and is consumed by the intracellular "respiratory engine" to provide the energy for metabolism. A defect at any point in the system—lungs, heart, blood, or tissues—can disrupt normal oxygenation and cause tissue damage or death of the organism.

In clinical practice a deficiency of oxygen in the arterial blood is commonly defined in relation to the oxyhemoglobin dissociation curve (Fig. 2).<sup>7</sup> Because of the sigmoid shape of the relationship between  $P_{aO_2}$  and  $S_{aO_2}$ , concern about arterial hypoxemia increases when  $P_{aO_2}$  is in the area of the "elbow" of the curve (at approximately 60–70 mm Hg), below which  $S_{aO_2}$  decreases more rapidly with further decrements in  $P_{aO_2}$ . Clinical concern intensifies as  $P_{aO_2}$  falls below 50–60 mm Hg and  $S_{aO_2}$  diminishes even more rapidly, and hypoxemic acute respiratory failure is generally considered to be present when  $P_{aO_2}$  is below 50 mm Hg.<sup>7</sup> However, although hypoxemia is probably the most common cause of life-threatening tissue hypoxia, this definition is too narrow.<sup>2</sup>

Table 2 lists the physiologic mechanisms of tissue hypoxia as encountered clinically. The table emphasizes the

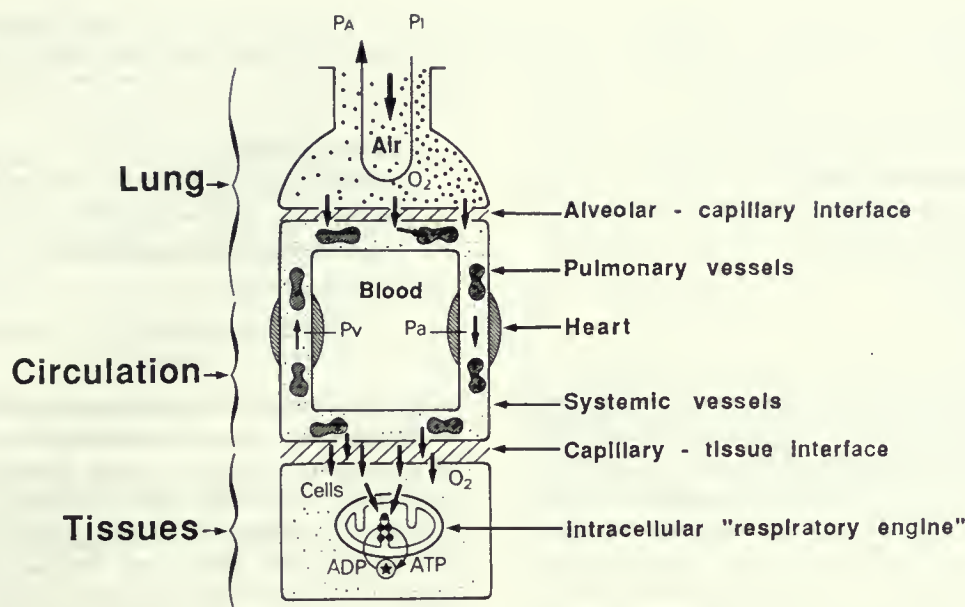


Fig. 1. Pathway for oxygen from outside air to ultimate consumption within the mitochondria of cells. Tissue hypoxia may result from an abnormality anywhere in the system, and its prevention or correction is the ultimate goal of supplemental oxygen therapy. Oxygen tensions in the diagram are inspired ( $P_i$ ), alveolar ( $P_A$ ), arterial ( $P_a$ ), and venous ( $P_v$ ). ADP = adenosine diphosphate. ATP = adenosine triphosphate. (Adapted from Reference 6, with permission.)

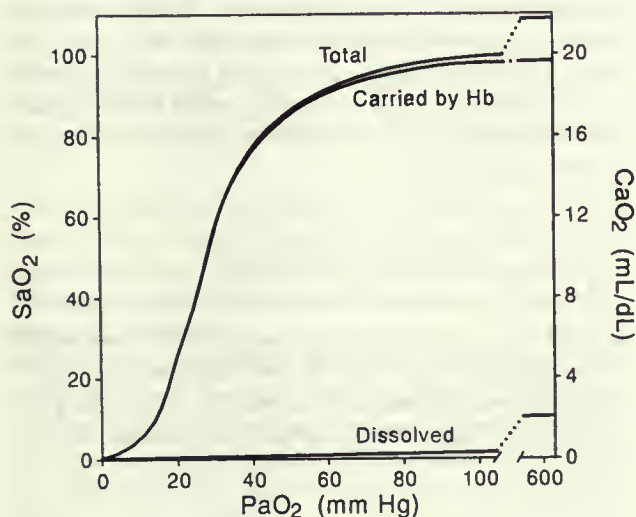


Fig. 2. Relationship of arterial oxygen tension ( $P_{aO_2}$ , horizontal axis) to oxyhemoglobin saturation ( $S_{aO_2}$ , left vertical axis) and arterial oxygen content ( $C_{aO_2}$ , right vertical axis) in the clinically relevant  $P_{aO_2}$  range (0–100 mm Hg) as well as at a  $P_{aO_2}$  of 600 mm Hg. The amount of oxygen dissolved in plasma is unimportant in most clinical settings, virtually all of it being bound to hemoglobin. The values for  $C_{aO_2}$  assume a normal blood hemoglobin concentration of 15 g/dL. (From Reference 7, with permission.)

potential role of mechanisms other than hypoxemia (that is, a low  $P_{aO_2}$ ). For example, life-threatening anemic hypoxia may be present in the face of a normal  $P_{aO_2}$ . In Figure 2 the right vertical axis shows the arterial oxygen content

( $C_{aO_2}$ ) corresponding to the  $S_{aO_2}$  associated with a given  $P_{aO_2}$  in a person with a normal blood hemoglobin concentration of 15 g/dL. Clinicians may assume that a normal  $P_{aO_2}$  means that tissue oxygenation is normal, but such is not necessarily the case. This is because, except under hyperbaric conditions, for clinical purposes  $C_{aO_2}$  is as high as it can get once the hemoglobin is fully saturated. With hemoglobin concentrations less than normal,  $C_{aO_2}$  must also be proportionally reduced. Figure 3 shows what the  $C_{aO_2}$  curve looks like when the hemoglobin concentration varies.<sup>7</sup> Even in the absence of hypoxemia, with  $S_{aO_2}$  100%,  $C_{aO_2}$  can be only about two thirds of normal with a hemoglobin concentration of 10 g/dL, and much less than that with more severe anemia.

Systemic oxygen delivery is the product of  $C_{aO_2}$  and cardiac output. Even when  $C_{aO_2}$  is normal, tissue oxygenation may be inadequate if cardiac function is impaired. The latter is commonly encountered both in the intensive care unit (as with cardiac failure or the application of excessive positive end-expiratory pressure<sup>2</sup>) and in the ambulatory care setting (as with chronic congestive heart failure). Reference to Figure 1 and Table 2 shows that impaired tissue oxygen utilization can also be a cause of oxygenation failure, even when systemic oxygen delivery is adequate. However, this mechanism is seldom encountered in the setting of chronic lung disease.

While it is important to remember the additional mechanisms for tissue hypoxia discussed above, arterial hypox-

Table 2. Mechanisms of Tissue Hypoxia

| Category                                 | Determinants                                                        |
|------------------------------------------|---------------------------------------------------------------------|
| Inadequate oxygenation of arterial blood |                                                                     |
| Hypoxemia                                | Decreased arterial $P_{O_2}$                                        |
| Inadequate arterial oxygen content       | Decreased $S_{aO_2}$ and/or hemoglobin concentration                |
| Inadequate systemic oxygen delivery      | Decreased $C_{aO_2}$ and/or cardiac output                          |
| Inadequate peripheral oxygen utilization | Impaired intracellular use and/or peripheral left-to-right shunting |

$P_{O_2}$  = oxygen tension.  $S_{aO_2}$  = arterial oxyhemoglobin saturation.  $C_{aO_2}$  = arterial oxygen content.

emia is the most common cause encountered in the long-term setting. Table 3 lists the four physiologic mechanisms of chronic arterial hypoxemia and provides clinical examples of each mechanism. Diffusion impairment is a fifth possible mechanism, although it occurs mainly during exercise at very high altitude and is not a significant contributor to hypoxemia as seen in patients with COPD. A reduction in the inspired  $P_{O_2}$  ( $P_{IO_2}$ ), as encountered at high altitude produces hypoxemia despite the normal function of all the components of respiration. In primary lung disease, hypoxemia is the result of one or more of the three remaining processes in the table—alveolar hypoventilation, ventilation-perfusion ratio ( $\dot{V}/\dot{Q}$ ) mismatching, and right-to-left shunting.

The most common mechanism for hypoxemia in patients with chronic pulmonary disease is mismatching of ventilation and perfusion, or, more accurately, an increase in low- $\dot{V}/\dot{Q}$  regions in the lung. Patients with COPD also often have a component of alveolar hypoventilation resulting from reduced carbon dioxide elimination in relation to

its production by the body, and determined by the presence of hypercapnia. Chronic hypoxemia due to right-to-left intrapulmonary shunting is rarely encountered, and this mechanism is generally not a significant contributor to hypoxemia in patients with COPD. That the latter is so is fortunate for both patient and clinician with respect to LTOT, because it means that hypoxemia in COPD is relatively easy to correct, as discussed below.

Knowing the mechanism or mechanisms of hypoxemia in a given patient is important in diagnosis, because different diseases produce hypoxemia in different ways and also in therapy, as hypoxemia caused by the different mechanisms responds differently to administration of supplemental oxygen and to other measures. To determine the mechanism or mechanisms of hypoxemia in a given patient, it is first necessary to estimate the alveolar-to-arterial  $P_{O_2}$  difference [ $P_{(A-a)O_2}$ ], commonly called the A-a gradient. Alveolar  $P_{O_2}$  ( $P_{AO_2}$ ) must first be determined using the alveolar gas equation:

$$P_{AO_2} = P_{IO_2} - P_{aCO_2}/R$$

wherein  $P_{aCO_2}$  is the arterial carbon dioxide tension and  $R$  is the respiratory quotient. In this equation, the  $P_{IO_2}$  is calculated from barometric pressure ( $P_B$ ), the partial pressure of water vapor ( $P_{H_2O}$ ) at body temperature, and the  $F_{IO_2}$ :

$$P_{IO_2} = (P_B - P_{H_2O}) \times F_{IO_2}$$

When breathing air at sea level,  $P_{IO_2}$  is:  $(760 - 47 \text{ mm Hg}) \times 0.21$ , or approximately 150 mm Hg. The respiratory quotient ( $R$ ), the overall ratio of  $CO_2$  produced to  $O_2$  consumed by the body, is about 0.8 for persons eating a usual North American mixed diet, and this assumed value is used in calculating  $P_{AO_2}$ . Thus, if the patient's  $P_{aCO_2}$  is 40 mm Hg:

$$P_{AO_2} = 150 \text{ mmHg} - 40 \text{ mmHg}/0.8 = 100 \text{ mmHg}$$

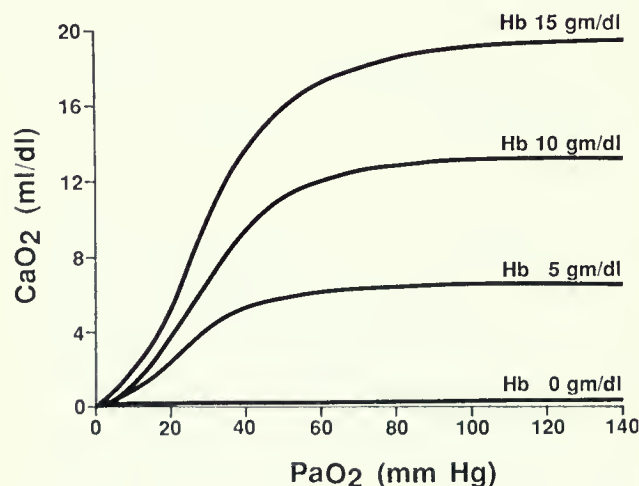


Fig. 3. Relationship of arterial oxygen content ( $C_{aO_2}$ ) to arterial oxygen tension ( $P_{aO_2}$ ) in the presence of different hemoglobin concentrations. Blood with 15 g/dL of hemoglobin contains 20 mL oxygen per 100 mL when fully saturated. Despite normal or even elevated  $P_{aO_2}$ , the blood of an anemic patient contains a markedly reduced amount of oxygen. (From Reference 7, with permission.)

Table 3. Mechanisms of Chronic Arterial Hypoxemia

| Physiologic Mechanism             | Clinical Examples                                                   |
|-----------------------------------|---------------------------------------------------------------------|
| Low inspired $P_{O_2}$            | Chronic mountain sickness                                           |
| Alveolar hypoventilation          | COPD with hypercapnia<br>Obesity hypoventilation syndrome           |
| Ventilation-perfusion mismatching | COPD<br>Pulmonary fibrosis<br>Most other chronic pulmonary diseases |
| Right-to-left shunting            | Arteriovenous malformation<br>Hepatopulmonary syndrome              |

$P_{O_2}$  = oxygen tension. COPD = chronic obstructive pulmonary disease.

Table 4. Practical Distinction Among the Main Mechanisms of Hypoxemia

| Physiologic Mechanism             | Clinical Findings                                                                                                               |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Alveolar hypoventilation          | Hypercapnia<br>Normal $P_{(A-a)O_2}$                                                                                            |
| Ventilation-perfusion mismatching | Increased $P_{A-a}O_2$<br>Good response to supplemental $O_2$<br>High $F_{IO_2}$ not required                                   |
| Right-to-left shunting            | Increased $P_{(A-a)O_2}$<br>Poor response to supplemental $O_2$<br>High $F_{IO_2}$ or PEEP may be required to correct hypoxemia |

$P_{(A-a)O_2}$  = alveolar-arterial oxygen gradient.  $F_{IO_2}$  = fraction of inspired oxygen. PEEP = positive end-expiratory pressure.

If this patient's  $P_{aO_2}$  were 85 mm Hg,  $P_{(A-a)O_2}$  would thus be  $100 - 85$  or 15 mm Hg. A  $P_{(A-a)O_2}$  value of less than about 20 mm Hg can be considered normal for clinical purposes, and a value greater than about 30 mm Hg is distinctly abnormal.

The different physiologic mechanisms of hypoxemia can be distinguished clinically using the patient's initial arterial blood gas results and the response to administration of supplemental oxygen (Table 4). If the patient is hypercapnic, alveolar ventilation is present by definition. In the presence of a normal  $P_{(A-a)O_2}$ , alveolar hypoventilation produces a fall in  $P_{aO_2}$  that is roughly equivalent to the increase in  $P_{aCO_2}$ .  $P_{aO_2}$  falls a bit more than the increase in  $P_{aCO_2}$  because the body consumes a greater quantity of  $O_2$  than the  $CO_2$  it produces, by the relationship R. This is illustrated in Figure 4,<sup>7</sup> which shows that  $P_{aO_2}$  and  $P_{aCO_2}$  change in opposite directions, assuming an unchanging  $P_{(A-a)O_2}$  and  $R = 0.8$ . An increase in  $P_{aCO_2}$  of 20 mm Hg will be associated with a fall in  $P_{aO_2}$  of about 25 mm Hg in an otherwise normal individual. Equivalent changes in the opposite direction occur with hyperventilation.

As shown in Table 4, alveolar hypoventilation (along with a low inspired  $P_{O_2}$ , not shown) causes hypoxemia

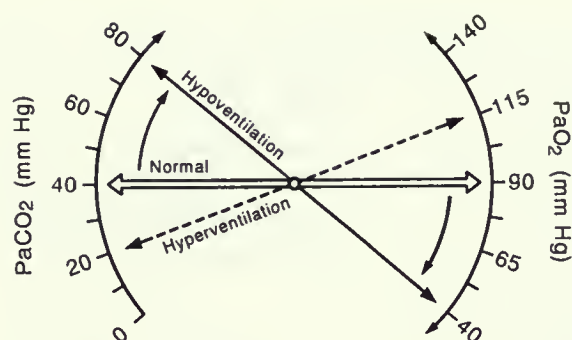


Fig. 4. Schematic depiction of how arterial oxygen and carbon dioxide tensions ( $P_{aO_2}$  and  $P_{aCO_2}$ , respectively) change in opposite directions, assuming an unchanging alveolar-to-arterial oxygen-tension difference ( $P_{(A-a)O_2}$ ) and a normal respiratory exchange ratio of 0.8. Alveolar hypoventilation raises the  $P_{aCO_2}$  above the normal value of 40 mm Hg and decreases  $P_{aO_2}$  proportionally. (From Reference 7, with permission.)

without increasing  $P_{(A-a)O_2}$ . Both  $\dot{V}/\dot{Q}$  mismatching and right-to-left shunting increase  $P_{(A-a)O_2}$ , but they can be distinguished for practical purposes by the response of  $P_{aO_2}$  to the administration of low-flow supplemental oxygen. If supplemental oxygen restores the  $P_{aO_2}$  to the normal range or substantially increases it,  $\dot{V}/\dot{Q}$  can be assumed to be the cause, while persistent hypoxemia implies the presence of very low  $\dot{V}/\dot{Q}$  areas, if not actual shunt. The clinical importance of this distinction is that high  $F_{IO_2}$ , positive end-expiratory pressure, or other measures may be required if the hypoxemia is caused by shunt, while  $\dot{V}/\dot{Q}$  mismatch causes hypoxemia that can easily be corrected. If both hypercapnia and an increased  $P_{(A-a)O_2}$  are present, then both alveolar ventilation and  $\dot{V}/\dot{Q}$  mismatching are contributing to the hypoxemia.

### Physiologic Responses to Hypoxia

JBS Haldane is said to have remarked that a lack of oxygen not only stops the machine but also wrecks the machinery. The correctness of this observation is manifestly apparent with acute, severe hypoxia as encountered in cardiopulmonary arrest or severe hypoxemic acute respiratory failure. However, in the context of this review the destructive effect of hypoxia on the machinery of the body is less dramatic and most often encountered in the form of altered function rather than structural damage.

In the 1960s it was shown that a  $P_{O_2}$  of at least 18 mm Hg is necessary to sustain mitochondrial function, and to generate adenosine triphosphate, which is essential for all major cellular biochemical functions.<sup>8</sup> Cellular hypoxia may be defined as a state in which convective or diffusive oxygen transport fails to meet the tissue demand for oxygen and when the rate of adenosine triphosphate synthesis becomes limited by the oxygen supply.<sup>9</sup> Decreases in ox-

Table 5. Physiologic Responses to Hypoxia

|                |                                                                                                                                    |
|----------------|------------------------------------------------------------------------------------------------------------------------------------|
| Respiratory    | Increased ventilation<br>Respiratory alkalosis                                                                                     |
| Cardiovascular | Pulmonary vasoconstriction<br>Pulmonary hypertension<br>Decreased maximum oxygen consumption<br>Decreased myocardial contractility |

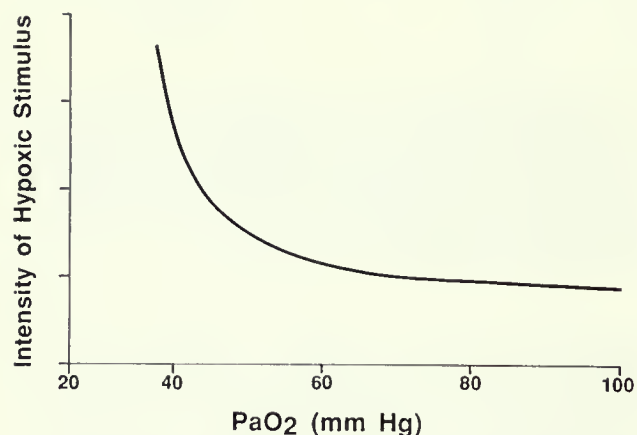


Fig. 5. General relationship between arterial oxygen tension ( $P_{aO_2}$ ) and hypoxic ventilatory drive. As  $P_{aO_2}$  falls below about 65 mm Hg in most normal individuals, hypoxic drive progressively increases its stimulus to breathe. The vertical axis depicts the intensity of the hypoxic stimulus, whether the individual is capable of increasing minute ventilation or prevented from doing so by airway obstruction or other disease process. (From Reference 12, with permission.)

xygen supply set in motion adaptive mechanisms designed to maintain cellular activity at a minimum acceptable level; the failure of these mechanisms during hypoxia results in cellular dysfunction and can lead to irreversible cell damage.<sup>10</sup> Discussion of hypoxia at the tissue and intracellular levels, the focus of much ongoing research,<sup>11</sup> is beyond the scope of this review.

Table 5 summarizes the normal responses of the respiratory and cardiovascular systems to hypoxia. In most instances these responses are compensatory and serve to prevent organ dysfunction or tissue damage that would otherwise occur. Differences among normal individuals in the presence and vigor of these responses probably account for much of the variation in clinical presentation observed in patients with chronic hypoxia caused by pulmonary disease.

### Respiratory System

The main respiratory response to hypoxia is an increase in hypoxic ventilatory drive, which in normal individuals results in increased ventilation (Fig. 5).<sup>12-14</sup> This response is to  $P_{aO_2}$ , not to  $S_{aO_2}$  or  $C_{aO_2}$ , and is mediated by the peripheral arterial chemoreceptors, located in the carotid

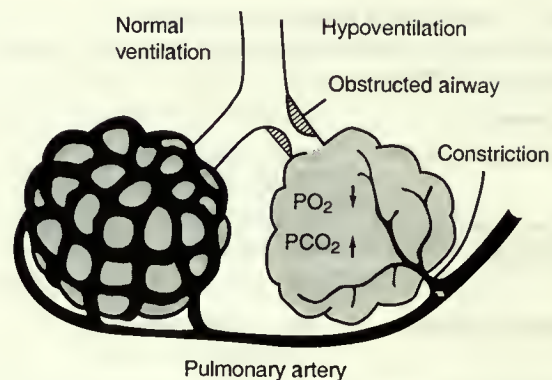


Fig. 6. In comparison to the situation in a normally oxygenated lung unit (left), hypoxic vasoconstriction (right) reduces blood flow to poorly ventilated regions, thus improving ventilation-perfusion matching. However, widespread hypoxic vasoconstriction increases overall pulmonary vascular resistance and thus the pressure required to maintain perfusion. (From Reference 18, with permission.)

bodies.<sup>13</sup> At sea level, ventilation is driven primarily by  $CO_2$  and by input from stretch receptors in the chest wall, so that only about 10% of the minute ventilation can be accounted for by hypoxic ventilatory drive. Regardless of whether ventilation or central drive is measured, the hypoxic response is curvilinear, unlike the linear response to hypercapnia. The vigor of the response, and thus the position and slope of the curve in Figure 5, is affected by  $P_{aCO_2}$ . Hypercapnia displaces the curve upward and to the right, whereas hypocapnia has the opposite effect.

Hypoxic ventilatory drive is diminished in a small proportion (less than 5%) of the normal population, and also in many highly successful athletes and after prolonged residence at high altitude. It declines with normal aging. It is also blunted in congenital cyanotic heart disease, in myxedema and severe hypothyroidism, in certain types of autonomic nervous system dysfunction, and with the chronic use of narcotics. Patients who have undergone carotid body resection, a now-abandoned procedure once performed as treatment for dyspnea in emphysema, also have blunted hypoxic ventilatory drive.

The increased ventilation associated with hypoxia is perceived as dyspnea by many individuals. Available evidence suggests that dyspnea in this context may also result in part from a direct stimulus of breathlessness,<sup>15</sup> although this appears highly variable among individuals. As with chronic hyperventilation in other settings, the normal response to prolonged hypoxia leads to compensatory metabolic acidosis produced by increased renal bicarbonate loss.

### Cardiovascular System

The most characteristic and important cardiovascular response to hypoxia is pulmonary vasoconstriction, which

reduces the caliber of pulmonary vessels and raises vascular resistance in a region of low alveolar  $P_{O_2}$ .<sup>16-18</sup> Hypoxic pulmonary vasoconstriction (HPV), first described a half century ago by Euler and Liljestrand,<sup>19</sup> serves to maintain  $\dot{V}/\dot{Q}$  matching in a localized area of airway obstruction or infiltration (Fig. 6),<sup>18</sup> but has a deleterious overall effect when alveolar hypoxia is widespread throughout the lung, as in chronic mountain sickness or COPD. Occurring primarily at the precapillary level and involving small muscular arteries and arterioles, and augmented by acidosis, HPV causes pulmonary hypertension and is a primary factor in the pathogenesis of cor pulmonale, as will be discussed later. The pulmonary vascular response to hypoxia occurs in two phases.<sup>20</sup> The first is the acute hypoxic vasoconstrictor response described above. When the hypoxia is prolonged for at least several weeks, a second phase consisting of vascular remodeling begins.

A variety of substances counteract HPV. In addition to inhalational anesthetics, these substances include prostacyclin and inhaled nitric oxide. Both of the latter agents have been used, at least experimentally, to treat chronic pulmonary hypertension.<sup>21</sup>

Severe hypoxia has a direct deleterious effect on cardiac function.<sup>9,22</sup> Myocardial contractility and maximum output are diminished during conditions of reduced oxygen supply.<sup>23</sup> While maximum oxygen consumption is reduced in chronic hypoxia, cardiac output remains normal at rest, owing primarily to an increased red blood cell mass.<sup>22</sup>

### Central Nervous System

Representing only 2–3% of an adult's body mass, the brain receives 20% of the cardiac output and accounts for about one fourth of overall resting oxygen consumption. The brain is one of the most oxygen-sensitive organs of the body, and it is not surprising that neurologic dysfunction is a prominent manifestation of hypoxia.<sup>24,25</sup> As discussed by Wedzicha elsewhere in this issue,<sup>26</sup> neuropsychiatric manifestations of chronic hypoxia can be a major source of morbidity in patients with COPD.

Cerebral vascular resistance is prominently affected by acute hypoxia, and increases when  $P_{aO_2}$  falls below 50–60 mm Hg.<sup>25</sup> However, with continued hypoxia, adaptation occurs, and overall cerebral blood flow in hypoxemic patients with COPD is normal. The brain is very sensitive to changes in perfusion, and effects of hypoxia on the brain are more likely to be due to decreased perfusion than to hypoxemia.<sup>25</sup>

### Adaptation to Altitude

At high altitude  $F_{IO_2}$  remains the same, but  $P_{IO_2}$  decreases as barometric pressure falls. In comparison with its value of about 150 mm Hg at sea level,  $P_{IO_2}$  is approxi-

mately 130 mm Hg at Denver's altitude of 5,280 feet and 80 mm Hg at 14,000 feet.<sup>27</sup> With acute ascent, as inspired oxygen tension falls, the body responds with a variety of physiologic adaptations to maintain adequate tissue oxygenation (Table 6). Stimulation of the peripheral arterial chemoreceptors results in increased ventilation, which occurs immediately.<sup>28</sup> Hypoxic pulmonary vasoconstriction also occurs concomitantly with the decrease in  $P_{IO_2}$ , increasing pulmonary vascular resistance and mean pulmonary arterial pressure. Acute hypoxia increases renal secretion of erythropoietin, which serves to augment peripheral oxygen delivery by increasing red blood cell mass, although this takes at least a week to become evident. Increased blood hemoglobin concentration occurs in the initial hours at altitude, however, due to hemoconcentration as a result of water diuresis.

Many otherwise healthy individuals experience acute mountain sickness within a day or two after ascent to altitudes above 8,000 feet, particularly if they arrived by air from sea level.<sup>27,29</sup> Symptoms include headache, lethargy, insomnia, anorexia, and in some cases nausea and vomiting. Believed to be due to mild cerebral edema, acute mountain sickness typically resolves over several days even if the individual remains at altitude. High altitude cerebral edema and high altitude pulmonary edema are more serious, sometimes fatal maladaptations of previously healthy individuals who ascend rapidly above 10,000–12,000 feet, which typically occur several days after arrival.<sup>27,30,31</sup> Chronic mountain sickness, described below, occurs in some individuals after months or years of residence at high altitude.

The maladaptations shown in Table 6 occur in individuals for whom the chronic hypoxia of residence at high altitude is something for which they are evolutionarily unprepared. There is evidence that evolution may be at work among peoples who have resided at altitude for thousands of generations to make them better adapted and less likely to suffer altitude-related illness.<sup>32,33</sup> Altitude illness is much more common among residents of the Colorado Rockies, where people of European ancestry have lived for less than 150 years, and also more common among the high altitude residents of the Andes, who have been there for up to several thousand years, than on the Tibetan Plateau, where the Tibetan peoples may have resided for a much longer period.<sup>32,33</sup> Compared with the two former groups, Tibetans have higher resting ventilation, stronger hypoxic ventilatory responses, lower hemoglobin concentrations, and increased cerebral blood flow with exercise.<sup>32</sup> Their resting pulmonary artery pressures are normal by sea level standards, and they exhibit only minimal HPV both at rest and during exercise.<sup>34</sup> In addition, Tibetans have less intrauterine growth retardation than high altitude residents of the Rocky Mountains and the Andes.<sup>32</sup>

Table 6. Adaptation and Maladaptation to High Altitude

| Minutes, Hours         | Days, Weeks                     | Months, Years               | Generations              |
|------------------------|---------------------------------|-----------------------------|--------------------------|
| Increased ventilation  | Increased RBC mass              | (Cor pulmonale)             | Increased HVR            |
| Increased PA pressures | (Acute mountain sickness)       | (Chronic mountain sickness) | Increased lung volumes   |
| Diuresis               | (High-altitude pulmonary edema) |                             | Increased cardiac output |
| Hemoconcentration      | (High-altitude cerebral edema)  |                             | Other adaptations        |

Maladaptations (altitude-related illness) are shown in parentheses. RBC = red blood cell. HVR = hypoxic pulmonary vasoconstriction. PA = pulmonary artery.

A natural experiment has been carried out in Tibet since that country was assimilated politically into China 50 years ago. A number of physiologic studies have been carried out in Lhasa (altitude 3,658 m) comparing the native Tibetans with Han (Chinese) residents, the latter having lived at altitude for only a few years.<sup>35-41</sup> These studies show that, compared with healthy Han residents of Lhasa, native Tibetans have increased resting ventilation,<sup>35</sup> increased hypoxic ventilatory response,<sup>35</sup> larger vital capacity,<sup>41</sup> and lower resting  $P_{aCO_2}$  and  $P_{(A-a)O_2}$ .<sup>41</sup> Tibetans also have less electrocardiographic evidence of right ventricular hypertrophy than do their Han counterparts.<sup>37</sup> From the results of these studies it can be concluded that the Tibetans are better adapted to life at altitude than are the Han, perhaps indicating evolutionary adaptation to chronic hypoxia over many generations.

### Symptoms and Signs of Hypoxia

The symptoms and signs of hypoxia (Table 7) are non-specific and similar to those of heart failure and several other conditions.<sup>42</sup> Although many patients with hypoxia are dyspneic, this is highly variable, and the clinical manifestations tend to be neurological and cardiovascular rather than respiratory. Similarly, although cyanosis is supposed to be present whenever there is more than 5 g/dL of deoxygenated hemoglobin, this sign varies enough from patient to patient and among different observers to be of little

clinical value in detecting hypoxemia. These observations emphasize the importance of the objective measurement of oxygenation in both diagnosis and treatment of hypoxia.

### Chronic Mountain Sickness

Chronic mountain sickness is a disorder affecting many long-term residents of altitudes above 9,000 feet.<sup>27,43,44</sup> It is similar in some ways to what is seen in COPD patients with chronic hypoxemia, although it does not involve airflow obstruction and has several features not generally observed in COPD.<sup>45</sup> As mentioned above, it occurs commonly in the Rockies and the Andes, but is uncommon among natives of the Himalayas and the Tibetan Plateau. Symptoms of chronic mountain sickness include lethargy, mental slowness, and decreased exercise capacity. Affected individuals are plethoric and usually have conjunctival injection and peripheral edema. Laboratory evaluation shows more severe hypoxemia and higher  $P_{aCO_2}$  than observed in others at the same altitude, along with erythrocytosis that may be profound, with hematocrit values of 75% or more.

The disorder is believed to result from maladaptation to high altitude, with relative hypoventilation, pulmonary hypertension, and cor pulmonale.<sup>43,44</sup> It becomes more common with increasing age,<sup>46</sup> and is more commonly seen in men than in women before menopause.<sup>47</sup> Treatment aims to relieve hypoxemia and blood hyperviscosity. Ideally, affected individuals should move permanently to a lower altitude, but this may not be an option for socioeconomic reasons. Similarly, LTOT is seldom available in the remote regions where chronic mountain sickness is prevalent. Staged phlebotomy is performed to maintain the hematocrit closer to the level expected for the altitude at which the patient lives.

### Hypoxia during Sleep

Although the subject of hypoxia during sleep is beyond the scope of this review, this phenomenon affects millions of people and has assumed increasing importance in recent years.<sup>48</sup> There is considerable overlap between COPD and sleep-disordered breathing.<sup>49-51</sup> The separate problem of nocturnal oxygen desaturation in patients who are not hy-

Table 7. Symptoms and Signs of Hypoxia

| Symptoms     | Signs                  |
|--------------|------------------------|
| (Dyspnea)    | (Respiratory distress) |
| Restlessness | (Cyanosis)             |
| Palpitations | Tachypnea              |
| Confusion    | Tachycardia            |
| Agitation    | Cardiac dysrhythmias   |
| Headache     | Hypertension           |
| Tremor       | Hypotension            |
| Asterixis    | Lethargy               |
| Diaphoresis  | Coma                   |

Symptoms and signs in parentheses are highly variable among individuals.

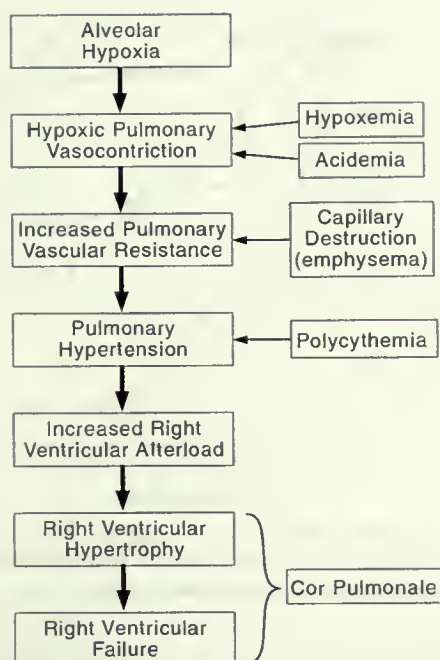


Fig. 7. Pathogenesis of cor pulmonale in chronic obstructive pulmonary disease. Long-term oxygen therapy attempts to reverse this process by eliminating alveolar hypoxia, the primary stimulus to increased pulmonary vascular resistance (PVR). However, as indicated in the diagram, the increased PVR is multifactorial, and only a partial reduction in pulmonary arterial pressures is achieved.

poxemic during the daytime<sup>52,53</sup> is discussed by O'Donohue in another paper from this conference.<sup>54</sup>

### Chronic Hypoxia in Chronic Obstructive Pulmonary Disease

#### Pathogenesis of Cor Pulmonale in Chronic Obstructive Pulmonary Disease

The term cor pulmonale refers to alterations in the structure and function of the right ventricle due to disease of the lungs rather than of the heart *per se*. More specifically, as defined by an expert committee of the World Health Organization, cor pulmonale is "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease."<sup>55</sup> The term cor pulmonale applies to patients who show evidence of structural change in the right ventricle, whether or not they have overt right-sided heart failure. However, it should not be used as a synonym for right heart failure, nor in patients with pulmonary hypertension who show no evidence of right ventricular hypertrophy.<sup>56</sup>

The pathophysiology of cor pulmonale in COPD, reviewed in a classic paper by Fishman,<sup>57</sup> has been revisited

more recently in a comprehensive review by MacNee.<sup>56,58</sup> The factors involved in its pathogenesis are depicted in Figure 7.<sup>59</sup> Alveolar hypoxia triggers HPV and its attendant increase in pulmonary vascular resistance. If the hypoxia is prolonged, the increased right ventricular afterload produced by the chronically elevated pulmonary artery pressure results in hypertrophy of the right ventricle. Eventually, if the process continues, overt right-sided heart failure ensues, with peripheral edema, hepatic congestion, and other signs of increased blood volume and elevated central venous pressure.

As suggested in the figure, the pathogenesis is not so straightforward as implied by the preceding description. Hypoxemia exerts an effect on the pulmonary vasculature separate from alveolar hypoxia, as does acidosis. Reduction in pulmonary capillary surface area caused by emphysema also contributes to the increased pulmonary vascular resistance. In addition, when present, erythrocytosis may further augment the pulmonary hypertension.

#### Clinical Manifestations of Hypoxia and Cor Pulmonale in Chronic Obstructive Pulmonary Disease

Just as the symptoms and signs of hypoxia are variable among individuals, the clinical manifestations of chronic hypoxia and cor pulmonale in patients with COPD show considerable variation. How dyspneic COPD patients with chronic hypoxemia are depends a lot on the severity of their airflow obstruction, but may also be a function of their underlying hypoxic ventilatory drive. The relationship between  $P_{aO_2}$  and the urge to breathe, as depicted in Figure 5, varies among normal individuals, as mentioned previously, with some small fraction of the population having markedly blunted hypoxic chemosensitivity. For individuals with COPD and normal or heightened underlying hypoxic drive, the development of hypoxemia would be expected to increase the severity of their dyspnea. Such individuals might seek to avoid hypoxemia by increasing ventilation insofar as they were capable of doing so. These patients would remain normoxic until very late in the course of their disease, but would be very dyspneic. On the other hand, it may be surmised that, for those individuals with naturally blunted hypoxic drives who develop COPD, hypoxemia might not stimulate additional breathlessness. Not being distressed by the development of chronic hypoxemia (with its attendant cyanosis), such individuals might develop cor pulmonale earlier than their normoxic, more dyspneic counterparts. These two extremes in clinical presentation—the "pink puffer" (also known as "Type A" COPD) and the "blue bloater" ("Type B") (Fig. 8)<sup>60</sup>—are atypical, but are consistent with present understanding of pathophysiology and illustrate the spectrum of clinical presentation in patients with chronic hypoxemia complicating COPD.



Fig. 8. Two patients with severe chronic obstructive pulmonary disease and comparable degrees of airflow obstruction, who illustrate two clinical extremes of the syndrome believed to be determined at least in part by how they respond to hypoxia. The "blue bloater" on the left has longstanding severe chronic hypoxemia and cor pulmonale but little dyspnea, whereas the "pink puffer" on the right maintains relatively normal oxygenation in the face of severe dyspnea. (From Reference 60, with permission.)

### Effects of Hypoxemia on Mortality in Chronic Obstructive Pulmonary Disease

Evidence for the effects of chronic hypoxia on mortality and morbidity in COPD is largely indirect. Early studies of the natural history of severe COPD<sup>61–63</sup> did not examine the separate influences of hypoxia, the severity of airflow obstruction, and other factors. However, by examining the findings of several large-scale studies some useful conclusions may be drawn about the impact of chronic hypoxia as a factor separate from other prognosticators.

Among patients with COPD, the more severe the pulmonary hypertension the worse the prognosis.<sup>64,65</sup> Figure 9 shows that 5-year survival among COPD patients with mean pulmonary artery pressures less than 25 mm Hg when initially examined is not very different from that

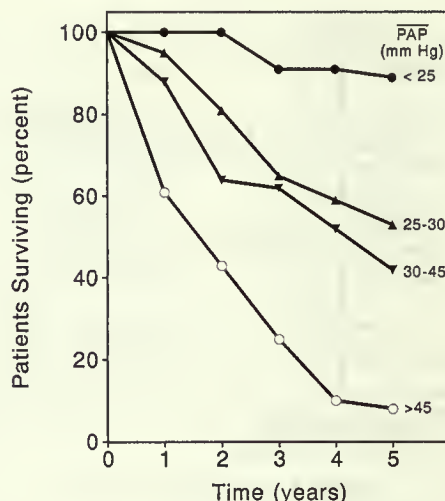


Fig. 9. Relationship between mean pulmonary arterial pressure (PAP) and survival in patients with chronic obstructive pulmonary disease. (From Reference 64, with permission.)

expected for persons of the same age. However, the prognosis worsens progressively with increasing mean pulmonary arterial pressure, and few patients with initial values exceeding 45 mm Hg survive 5 years. The data in Figure 9<sup>64</sup> do not take the severity of airflow obstruction into account, and no doubt those individuals who fared best also tended to have less severe disease. As previously discussed, hypoxia is also not the only factor contributing to pulmonary hypertension in these patients, and LTOT does not restore pulmonary arterial pressures to normal.<sup>64–66</sup> However, the data in the figure provide strong evidence for an important impact of the magnitude of pulmonary hypertension on survival in patients with COPD.

Studies have attempted to correlate numerous anatomic, spirometric, imaging, and functional measurements with survival in COPD patients. Of these, the forced expiratory volume in the first second (FEV<sub>1</sub>) remains the best single assessment of functional impairment and predictor of survival.<sup>61,67</sup> Burrows<sup>61</sup> performed a long-term follow-up study on 200 patients with COPD and showed a clear separation into survival groups according to initial FEV<sub>1</sub> (Fig. 10). Half of all patients with initial FEV<sub>1</sub> values exceeding 1.25 L were alive 10 years after starting the study, while 75% of those with initial FEV<sub>1</sub> values less than 750 mL were dead within 5 years.<sup>61</sup>

Chronic hypoxia increases mortality regardless of the severity of airflow obstruction.<sup>68,69</sup> Thus, each of the curves in Figure 10 is shifted downward by the presence of chronic stable hypoxemia. The Nocturnal Oxygen Therapy Trial (NOTT)<sup>70</sup> and British Medical Research Council (MRC) multicenter study of LTOT<sup>71</sup> demonstrated that LTOT improved survival in patients with COPD and chronic stable hypoxemia. In the NOTT, patients who used oxygen only at night had a significantly poorer survival over the three

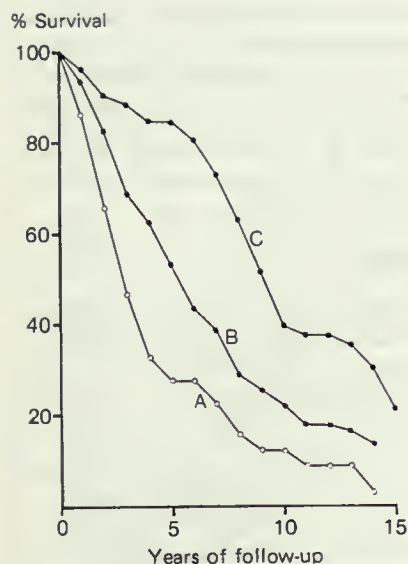


Fig. 10. Relationship of severity of airflow obstruction, as measured by forced expiratory volume in the first second ( $FEV_1$ ), to survival in 200 patients with chronic obstructive pulmonary disease followed prospectively for 15 years. Group A ( $n = 58$ ) had initial  $FEV_1$  values of  $< 750$  mL; Group B ( $n = 90$ ) 750–1,250 mL; and Group C ( $n = 52$ )  $> 1,250$  mL. (From Reference 60, with permission.)

years of the study than patients assigned to continuous oxygen use.<sup>70</sup> Using data from the NOTT study and also the results of the Intermittent Positive Pressure Breathing Trial (IPPB),<sup>72</sup> Anthonisen et al were able to demonstrate the downward shift of the survival curve due to chronic hypoxia for a given degree of airflow obstruction.<sup>68,69</sup> Patients included in the IPPB study had COPD but had to be normoxemic as a criterion for inclusion. Anthonisen et al matched patients in the IPPB study, the nocturnal-only oxygen arm of the NOTT, and the continuous oxygen arm of the NOTT for degree of airflow obstruction as measured by  $FEV_1$ . They found that survival was the same for the IPPB patients and the continuous-oxygen NOTT patients, and better than for the nocturnal-oxygen NOTT patients (Fig. 11).<sup>68</sup> Thus, COPD patients with the same severity of disease as measured by  $FEV_1$  had worse survival if they were hypoxemic and the hypoxemia was relieved only about half the time, whereas chronic hypoxemia did not worsen survival if oxygen was used most of the time.

The MRC and NOTT studies show that, with respect to survival, for COPD patients with stable chronic hypoxemia, some oxygen every day is better than none, but more oxygen is better yet. Survival in the MRC oxygen group and in the NOTT nocturnal-only group was approximately the same (and better than in the MRC no-oxygen group), but survival in the NOTT continuous-oxygen group was substantially better than in either of them. The NOTT included measurements of actual oxygen use by the pa-

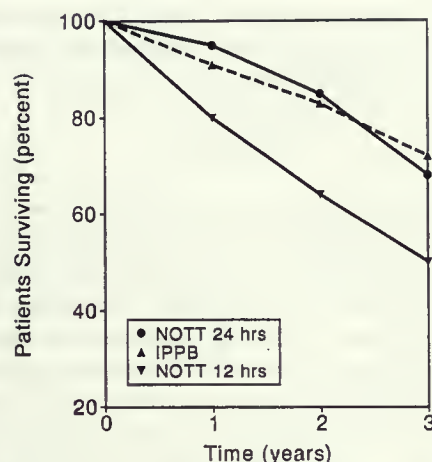


Fig. 11. Effect of hypoxemia on survival in patients under 65 years of age with chronic obstructive pulmonary disease and comparable severity of airflow obstruction, as determined from results of the Nocturnal Oxygen Therapy Trial (NOTT) and the Intermittent Positive Pressure Breathing Trial (IPPB). Hypoxemic patients treated with oxygen only at night (triangles, solid line) had worse survival than either nonhypoxemic patients (triangles, dashed line) or hypoxemic patients treated with continuous oxygen (circles, solid line). (Adapted from Reference 64, with permission.)

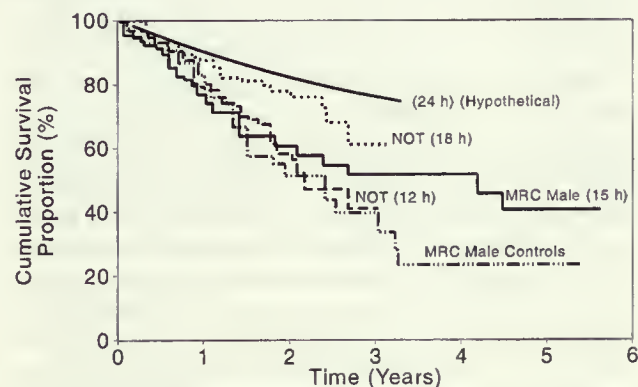


Fig. 12. Dose-response relationship between daily hours of use and survival in chronically hypoxemic patients with chronic obstructive pulmonary disease treated with long-term oxygen therapy, as extrapolated from the Nocturnal Oxygen Therapy Trial (NOTT) and the British Medical Research Council Study (MRC). Patients in the NOTT continuous oxygen therapy group (actual use averaging 18 h/d) had better survival than those in the MRC oxygen group (15 h/d) and those in the NOTT nocturnal group (average use 12 h/d), and all oxygen-treated patients fared better than the MRC no-oxygen group. Although it has not been shown experimentally, it may reasonably be hypothesized that true 24 h/d use would increase survival even more.

tients, and showed that the continuous-oxygen patients actually used their oxygen on average only about 18 h/d. Based on the dose-response relationship inferred from combining the results of the two studies, it may be hypothesized that true 24 hour-per-day oxygen use would have improved survival to an even greater extent (Fig. 12). There is no direct

evidence in support of this hypothesis, but it provides a rationale for encouraging patients who qualify for LTOT to use their oxygen as much of the time as possible.

### Summary

Hypoxia exists when there is a reduced amount of oxygen in the tissues of the body. Hypoxemia refers to a reduction in  $P_{O_2}$  below the normal range, regardless of whether gas exchange is impaired in the lung,  $C_{aO_2}$  is adequate, or tissue hypoxia exists. There are several potential physiologic mechanisms for hypoxemia, but in patients with COPD the predominant one is  $\dot{V}/\dot{Q}$  mismatching, with or without alveolar hypoventilation, as indicated by  $P_{aCO_2}$ . Hypoxemia caused by  $\dot{V}/\dot{Q}$  mismatching as seen in COPD is relatively easy to correct, so that only comparatively small amounts of supplemental oxygen (less than 3 L/min for the majority of patients) are required for LTOT. Although hypoxemia normally stimulates ventilation and produces dyspnea, these phenomena and the other symptoms and signs of hypoxia are sufficiently variable in patients with COPD as to be of limited value in patient assessment.

Chronic alveolar hypoxia is the main factor leading to development of cor pulmonale—right ventricular hypertrophy with or without overt right ventricular failure—in patients with COPD. Pulmonary hypertension adversely affects survival in COPD, to an extent that parallels the degree to which resting mean pulmonary artery pressure is elevated. Although the severity of airflow obstruction as measured by  $FEV_1$  is the best correlate with overall prognosis in patients with COPD, chronic hypoxemia increases mortality and morbidity for any severity of disease. Large-scale studies of LTOT in patients with COPD have demonstrated a dose-response relationship between daily hours of oxygen use and survival. There is reason to believe that continuous, 24-hours-per-day oxygen use in appropriately selected patients would produce a survival benefit even greater than that shown in the NOTT and MRC studies.

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## Discussion

**Petty:** David, it's a fact that FEV<sub>1</sub> is a good prognostic indicator, and it's the better prognostic indicator if made

age-specific. That is, at what age your FEV<sub>1</sub> is abnormal, and is it reversible? And that becomes the indicator for early identification and intervention. That's the reason why we have

such a passion today for the National Lung Health Education program, because our real challenge now is to deal with early stages of disease, and I have a pin for most of you called

"The Second Breath of Life." The first breath of life, of course, is the baby's breath that allows the child to live in the first place, and the second breath of life is your spirogram during adulthood that tells how long you're probably going to live.

**O'Donohue:** Dave, in your definition of hypoxemia as decreased oxygen in the blood, would you consider someone who is anemic to be hypoxemic since they have decreased oxygen in the blood, or is it strictly the  $P_{O_2}$ ?

**Pierson:** *Dorland's*, from which I took that (and I surveyed a number of other dictionaries as well), gives us a number of different kinds of hypoxia. There's anemic hypoxia, stagnant hypoxia, hypoxic hypoxia, histotoxic hypoxia, and one or two others, and they would describe anemic hypoxia as that due to insufficient delivery of oxygen by virtue of not enough. . .

**O'Donohue:** Hypoxemia is the term to which I am referring, not hypoxia.

**Pierson:** Hypoxemia. Here I've not been able to find unanimous agreement. For example, *Stedman's Medical Dictionary* says hypoxemia is deficient oxygen in the arterial blood, whereas *Dorland's* doesn't specify the condition of the blood. I have always used the definition that hypoxemia means that your  $P_{O_2}$  is abnormally low. So, if I'm breathing 100% oxygen, and I have acute respiratory distress syndrome (ARDS) and am on a ventilator, and my  $P_{O_2}$  is 80, I am not hypoxemic. Likewise, if my hemoglobin is only 5, I may have an oxygen content that's only a third of normal, but I'm not hypoxemic by that convention. But I think that it's difficult to find a universally-agreed-upon identification. Does that agree with your concept, Walter?

**O'Donohue:** Yes, absolutely. I have always personally used the term to mean a decreased  $P_{O_2}$ . Patients with severe anemia have decreased oxygen

content, but I have never referred to them as being hypoxemic.

**Pierson:** It would be a shame if we couldn't at least agree on the ABC's for our discussion for these next two and a half days.

**O'Donohue:** But in both cases they have decreased oxygen in the blood.

**Stoller:** David, I thought it was a wonderful talk. At the risk of being a splitter, I just want to comment on your use of the hepatopulmonary syndrome as an example of right-to-left shunt, and lumping it with arteriovenous malformation. Regarding your self-acknowledged 20-year-old slide about the 5 mechanisms of hypoxemia (eg,  $\dot{V}/\dot{Q}$  mismatch and so on), some authors have suggested that the hepatopulmonary syndrome represents an unusual admixture of diffusion impairment and right-to-left shunt, such that some authors have actually added a sixth cause of hypoxemia called diffusion-perfusion impairment. In the hepatopulmonary syndrome, there is dilatation of the capillaries causing the unusual circumstances in which blood is passing very quickly through dilated capillaries. This creates an impediment to diffusion of oxygen to the very center of the stream, which partially corrects with supplemental oxygen, albeit incompletely.<sup>1,2</sup> So, at the risk of being a nitpicker about that issue, we should mention diffusion-perfusion impairment as another physiologic cause of hypoxemia, to make the list complete.

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**Pierson:** I'm glad you brought that up, Jamie, because I'm ready for you! In ARDS, the studies back in the 1970s by Dantzker<sup>1</sup> and, subsequently, by

the group in Seattle,<sup>2</sup> using the multiple inert gas elimination technique, showed that, in fact the "shunt" in ARDS was predominantly very low  $\dot{V}/\dot{Q}$  areas. And that has been demonstrated in a lot of other situations where there isn't purely an anatomical connection such as in arteriovenous malformation. The reason I left those things off is that I think it helps the clinician's understanding to have the concept that hypoxemia in certain clinical settings behaves as if it were shunt, which in other clinical settings behaves as if it were  $\dot{V}/\dot{Q}$  mismatching. The physiologist may be able to demonstrate to us that there's a little bit more to it than that, but I don't believe that's of much help to the clinician at the bedside who is faced with relieving the hypoxemia, who doesn't really care whether ARDS is very low  $\dot{V}/\dot{Q}$  areas or shunt, because it gets better when you use positive end-expiratory pressure, and it won't get better unless you do something physical like that. So, with apologies for the specifics of accuracy, that is the reason I left that out.

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**McCoy:** I've got a practical sort of question for you, about the fact that long-term oxygen therapy is mostly delivered in the home setting. The people who manage the reimbursement for home oxygen therapy seem to not understand the question of the effects of hypoxemia, and come back with a "So what?" It seems that most of the research shows that *survival* is the "So what?" answer. To a payer, as bad as it sounds, "So what?" with someone not surviving costs less. One of the things they need to understand is what the cost and consequences are of some-

one who is not treated correctly for their disease with regard to hospitalization, doctor's visits, medication, other modalities, and just exactly what is involved in that process so that they can better understand the "So what?"

**Pierson:** I think that's an excellent observation, and in my discussion of the clinical effects, if you will, of chronic hypoxia, I should include the effects on the person, the effects on the family, and the effects on the health care system, because, in fact, chronic hypoxia extracts an enormous cost. This gets back to something Tom was saying about plopping those medical records down on the desk of the state health administrator. I think that's a very well-made point.

**Zielinski:** David, you mentioned that you had no time to develop in detail as many items as you talked about. May I add some data on adaptation of Tibetans, who are the only population, I think, who adapted very well to the conditions of living at high altitude. It was found that Tibetans do not react to hypoxia with pulmonary vasoconstriction. Of course, it is very difficult to perform pulmonary catheterization in those people. Five young Tibetans—lifelong residents of Lhasa—agreed to have pulmonary artery catheterization with hemodynamic measurements taken at rest, breathing hypoxic mixture, and on exercise. At rest, pulmonary arterial pressure was perfectly normal ( $15 \pm 1$  mm Hg). Pulmonary vascular resistance was also normal. Breathing hypoxic mixture lowering their  $P_{aO_2}$   $36 \pm 2$  mm Hg only slightly increased pulmonary vascular resistance. These data suggest that Tibetans lost hypoxic pulmonary vasoconstriction and remodeling common to lowlanders and residents of the Andes in South America.<sup>1</sup> Also in China there is the High Altitude Medical Research Institute. Professor Tianyi Wu, director of the institute, had an opportunity to catheterize 3 or 4 healthy Tibetans.

They also had normal pulmonary arterial pressure despite living at altitude of some 4,000 meters (personal communication). In a study comparing working capacity at high altitude of trained lowlanders and Sherpas, the latter showed superior work capacity. This was attributable to (1) economy of ventilation with preservation of normal blood pH, (2) a very high lung diffusing capacity for oxygen, and (3) a high cardiac output relative to work intensity.<sup>2</sup> Lifelong Tibetan residents of Lhasa (3,658 m) had higher hypoxic ventilatory response and minute ventilation than acclimatized Han Chinese coming from lowlands.<sup>3</sup>

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**Pierson:** I go into considerably more detail about these things in my paper. A natural experiment has been done since Tibet was absorbed into China politically about 50 years ago, in that there is now a large population of Han Chinese living with the Tibetans in Tibet. The Han have now been there for up to 50 years, whereas the Tibetans have been there perhaps as much as a million years. Comparative studies of those two populations<sup>1–4</sup> show a number of striking differences. For example, failure to carry pregnancies to term is much more prevalent in the Han Chinese (as are low birth weight, pulmonary hypertension, and a number of the clinical maladies associated with living at high altitude) than in the Tibetans. This may be an example of evolution at work even within a single species.

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**Spratt:\*** A question on the treatment of nocturnal hypoxemia. I believe right now the American Thoracic Society standards for chronic obstructive pulmonary disease<sup>1</sup> suggest treatment only if you have signs and symptoms of cor pulmonale. From Fletcher's work<sup>2</sup> and from what we know from obstructive sleep apnea patients developing pulmonary hypertension, a part of the pulmonary hypertension is going to be nonreversible. Are we waiting too late to treat those people if we're waiting for signs and symptoms of cor pulmonale, and is there a way we can predict those patients who are more likely to develop those long-term problems so we can treat them earlier?

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**Pierson:** We thought that was such an important question that we devoted an entire presentation to it. Walter's going to give that presentation, and I look forward to the answers to those questions.

\*Greg Spratt, Rotech Medical Corporation, Kirksville, Missouri.

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# Adverse Effects of Low-Flow Oxygen Therapy

Joshua O Benditt MD

## Introduction

### Tissue Toxicity

#### Clinical Manifestations of Tissue Oxygen Toxicity

### Respiratory System Toxicity

#### Tracheobronchitis

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#### Acute Parenchymal Lung Injury

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### Summary

[Respir Care 2000;45(1):54–61] *Key words: low-flow oxygen therapy, oxygen hazard, oxygen toxicity, absorption atelectasis, parenchymal lung injury, hypercarbia, fire hazard, oxygen cylinder, oxygen concentrator, liquid oxygen.*

## Introduction

The British scientist Joseph Priestley first produced oxygen in 1774 by heating mercuric chloride.<sup>1</sup> Lavoisier, who thought (mistakenly) that the gas was an essential component in acid formation, named it oxygen from the Greek terms “oxy” (acid) and “gen” (to form). Almost from the time of its discovery excess oxygen was thought to be toxic to organisms, but the first documentation of oxygen toxicity was by Paul Bert, who described oxygen toxicity to the central nervous system.<sup>2</sup> In 1899 J Lorain Smith described lethal pulmonary pathology in animals exposed to a fraction of inspired oxygen (0.75–1.0) for 4 days.<sup>3</sup> It was clear from these early studies that there was

a critical level of oxygen necessary for survival —enough to supply important metabolic processes but not so much as to injure the organism. This concept is illustrated in Figure 1. Since the early descriptions of oxygen toxicity it has been learned that hyperoxia can have adverse effects on many types of tissues (Table 1). In addition to *direct tissue toxicity*, the major adverse effects of oxygen therapy are *maladaptive physiologic responses* (eg, hypercarbia) and *nonmedical adverse effects* (eg, oxygen therapy-related fires). This review evaluates these adverse effects in detail.

## Tissue Toxicity

### Clinical Manifestations of Tissue Oxygen Toxicity

Oxygen is an essential component in many biologic reactions. Toxicity is thought to occur only with exposure to elevated inhaled partial pressure of oxygen. The toxicity of oxygen is dose dependent and is related to both the

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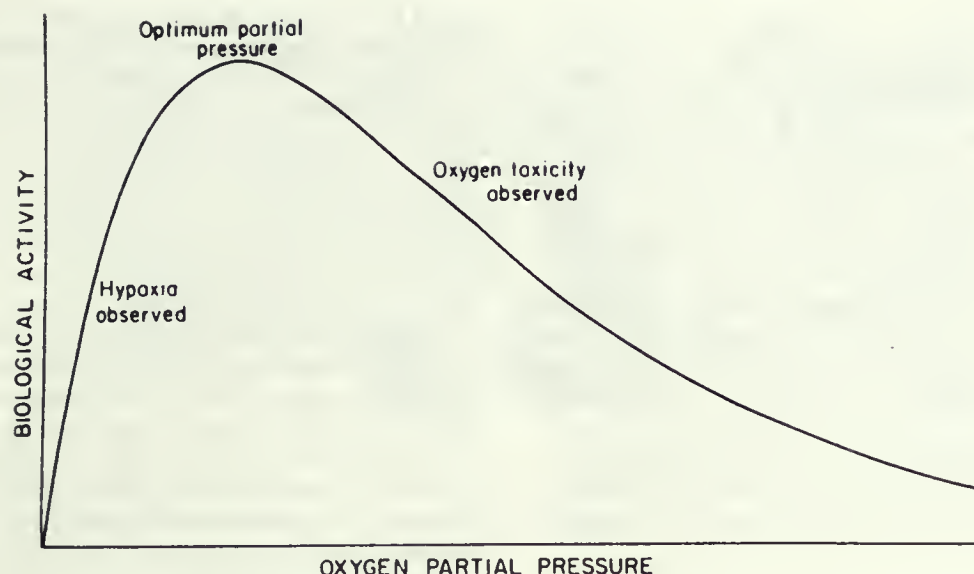


Fig. 1. Dual effect of oxygen biologic activity. (From Gibert DL. Oxygen: An overall biological view. In Oxygen and living processes. New York: Springer-Verlag, 1981: 376-392, with permission.)

Table 1. Organ System Toxicities Seen in Response to Exposure to High Levels of Inspired Oxygen

| Organ System    | Clinical Manifestations      |
|-----------------|------------------------------|
| Central nervous | Twitching                    |
|                 | Confusion                    |
|                 | Seizure                      |
|                 | Neuronal cell death          |
|                 | Death                        |
| Respiratory     | Tracheobronchitis            |
|                 | Absorption atelectasis       |
|                 | Parenchymal damage           |
|                 | Acute                        |
|                 | Diffuse alveolar damage      |
|                 | Chronic                      |
| Ocular          | Bronchopulmonary dysplasia   |
|                 | Chronic parenchymal scarring |
|                 | Retina damage/blindness      |
| Renal           | Myopia                       |
|                 | Tubular cell injury          |
| Hematologic     | Hemolysis                    |
| Cardiovascular  | Myocyte injury               |

inhaled partial pressure of oxygen and the duration of exposure. All tissues are susceptible to toxic effects from excessive oxygen exposure,<sup>4</sup> although the sensitivity of each tissue to hyperoxic injury varies significantly. The central nervous system appears to be injured only when hyperoxia occurs at elevated atmospheric pressures (hyperbaric hyperoxia), but other tissues, such as lung tissues, are susceptible to oxygen toxicity at ambient pressure (normobaric hyperoxia) (Fig. 2). The mechanism of differential tissue response to hyperoxic injury is not clearly defined

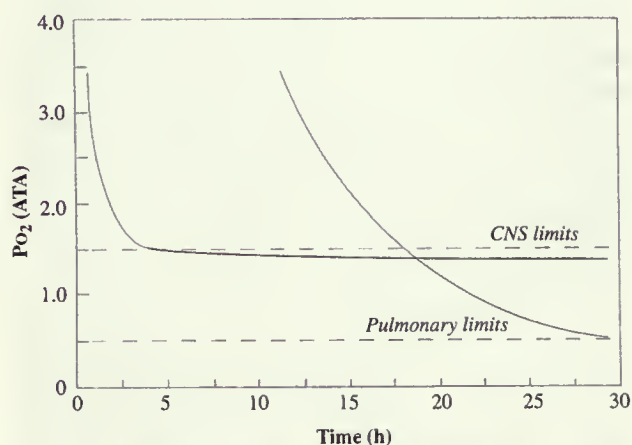


Fig. 2. Concentration-time relationships for appearance of oxygen toxicity. Hypothetical curves for central nervous system (CNS) and lungs are shown.  $P_{O_2}$ (ATA) = partial pressure of oxygen (atmospheres absolute). (From Reference 6, with permission.)

but probably depends on the normal oxygenation level of the tissue, the cell-specific biochemistry, and the antioxidant defenses of the specific tissue.<sup>4,5</sup> Several recent reviews of tissue oxygen toxicity are available.<sup>6,7</sup>

### Respiratory System Toxicity

Oxygen toxicity in the respiratory system has been described in 4 forms: (1) tracheobronchitis, (2) absorption atelectasis, (3) acute parenchymal lung injury, and (4) chronic parenchymal lung injury.

## Tracheobronchitis

The syndrome of acute tracheobronchitis on exposure to high levels of inhaled oxygen was first described by Comroe et al in 1945,<sup>8</sup> who reported cough, sore throat, and substernal burning in normal subjects breathing a fraction of inspired oxygen ( $F_{IO_2}$ ) of either 0.75 or 1.0 for 24 hours, but not in those receiving an  $F_{IO_2}$  of 0.5. Substernal burning was the first symptom noted and began as early as 4 hours after the initiation of breathing oxygen-enriched gas. Sackner reported direct visual evidence of tracheobronchitis assessed by fiberoptic bronchoscopy in studies of normal subjects breathing 100% oxygen for 6 hours.<sup>9</sup> They noted tracheobronchial inflammation as well as a significant decrease in mucous velocity, thought to be consistent with impairment of mucociliary function. These findings were reversible when the subject returned to breathing room air.

## Absorption Atelectasis

Inhalation of 100% oxygen (both by normal subjects and patients with lung disease) increases the alveolar-arterial oxygen gradient, results in infiltrates visible on chest roentgenogram, and causes progressive loss of vital capacity as measured by spirometry. Atelectasis is thought to occur in alveolar-capillary units with low ventilation-perfusion ratios.<sup>10</sup> In that case, absorption of gas from alveoli exceeds the rate of replenishment during inspiration, resulting in progressive volume loss and collapse of alveoli. This does not occur while breathing room air because nitrogen, an inert gas, is present in both alveoli and blood in equilibrium and prevents alveolar collapse. Absorption atelectasis depends on the ventilation-perfusion ratio of the alveolar-capillary units, the pattern of ventilation, the duration of exposure to high  $F_{IO_2}$ , and the intrinsic stability of the lung units (surfactant and tissue factors).<sup>7</sup> This effect is reversed by breathing room air. The clinical manifestations of atelectasis are a progressive decrease in arterial oxygen tension despite maintaining an  $F_{IO_2}$  of 1.0, fever, and pulmonary infiltrates and volume loss visible on chest radiograph.

## Acute Parenchymal Lung Injury

Acute hyperoxic injury to parenchymal lung tissue is best characterized in animal models of oxygen toxicity.<sup>11</sup> The pathologic process of hyperoxic parenchymal toxicity is divided into an earlier *exudative stage* (characterized by cellular damage, edema, and hyaline membrane formation) and a later *proliferative stage* (characterized by alveolar lining cell hyperplasia and septal fibrosis).<sup>7</sup>

In the exudative stage, endothelial cells in lung capillaries are the first cells to show the toxic effects of ele-

vated  $F_{IO_2}$ . Damage to these cells leads to edema in the pericapillary space and release of inflammatory mediators stimulating recruitment of inflammatory cells and platelets into the interstitium, alveolar spaces, and capillaries.<sup>12</sup> Portions of the capillary are destroyed,<sup>11</sup> and Type I alveolar cell damage,<sup>12</sup> alveolar wall fragmentation, and intra-alveolar edema also occur. Fibrinous hyaline membranes form in alveoli, alveolar ducts, and terminal bronchioles, and are thought to be the pathologic lesion that correlates most closely with hyperoxic lung injury.

The proliferative stage of hyperoxic lung injury is thought to represent a lung repair process.<sup>6</sup> Destroyed Type I pneumocytes are replaced by Type II pneumocytes,<sup>13</sup> and remaining capillary endothelial cells hypertrophy, resulting in thickening of capillary walls and a decrease in capillary lumen cross-sectional area that can result in microvascular thrombosis.<sup>14</sup> Interstitial fibroblasts are activated, possibly by fibronectin and macrophage-derived growth factor,<sup>15</sup> and may lead to fibrosis and scarring. In nonhuman primate models, proliferative changes have been noted for weeks after exposure to even the modest  $F_{IO_2}$  of 0.6 for 14 days.<sup>11</sup>

Whether acute hypoxic parenchymal lung injury occurs in humans is a topic of some debate. The clinical syndrome of pulmonary infiltrates, fever, and progressive arterial hypoxemia associated with a histopathology picture of diffuse alveolar damage is difficult to distinguish from acute lung injury due to other processes, including acute respiratory distress syndrome. Demonstrating an independent causal effect of hyperoxia has been difficult, because it is in the latter clinical situations in which a clinician is most likely to use potentially injurious levels of inspired oxygen. Prolonged exposure of normal humans to high levels of oxygen is unusual but case reports are available. Barber et al reported finding bilateral progressive pulmonary infiltrates in comatose patients exposed to 100% oxygen over several days prior to death.<sup>16</sup> Hyde and Rawson reported scattered patchy pulmonary infiltrates, leukocytosis, fever, and no clear cause of infection in 5 patients with neuromuscular disease who were inadvertently exposed to an  $F_{IO_2}$  of 0.85–1.0.<sup>17</sup> The findings resolved when oxygen levels were returned to normal. Despite the results of these intriguing “accidental” experiments, the degree to which acute parenchymal oxygen toxicity occurs in day-to-day clinical practice in the intensive care unit is currently unknown.

## Chronic Parenchymal Lung Injury

In most cases it appears that the clinical and histologic changes that result from oxygen toxicity are reversible.<sup>18,19</sup> However, there are two instances where the histologic changes induced by oxygen toxicity are reported to be irreversible: bronchopulmonary dysplasia and chronic parenchymal injury.

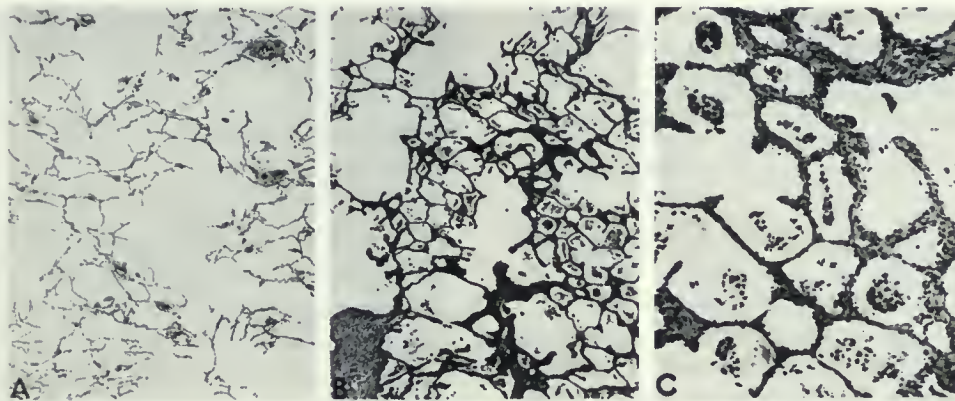


Fig. 3. A: Mild alveolar septal destruction by emphysema and slight arteriolar thickening. No features attributable to oxygen toxicity. (Hematoxylin and eosin; original magnification  $\times 30$ .) B: Coarsening of alveolar septa and of interstitium generally. (Hematoxylin and eosin; original magnification  $\times 30$ .) C: Detail from Figure 3B, showing proliferated alveolar epithelium, luminal macrophages, and interstitial hypercellularity. The interstitial infiltrate is composed of lymphocytes, histiocytes, plasma cells, and fibroblasts. (Hematoxylin and eosin; original magnification  $\times 80$ .) (From Reference 22, with permission.)

**Bronchopulmonary Dysplasia.** Bronchopulmonary dysplasia is a disorder that occurs in newborns with respiratory distress syndrome who are exposed to high levels of oxygen and elevated inflation pressures during mechanical ventilation. It is not known which of those two etiologic factors plays the major role, but it is clear that high levels of oxygen contribute to the pathology. Characteristic histologic features include abnormalities of the bronchioles, including metaplasia, obliteration, and cystic changes. Bronchopulmonary dysplasia may be associated with chronic respiratory difficulties, recurrent hospitalization, and even delayed growth. A small number of cases have been reported in adults who have a clinical picture typical of acute respiratory distress syndrome but radiographic and histopathologic findings consistent with bronchopulmonary dysplasia.<sup>20</sup> The incidence of this process in adults is unknown.

**Chronic Parenchymal Injury.** The degree of oxygen-induced damage to lung parenchyma depends on the partial pressure of inhaled oxygen to which the lung is exposed and the duration of exposure. Whereas exposure to hyperbaric oxygen results in clinically measurable changes in animals and humans within hours, it is commonly held that exposure to an  $F_{IO_2}$  of  $< 0.5$  can be tolerated for weeks or longer.<sup>21</sup> The lowest  $F_{IO_2}$  that can be safely tolerated indefinitely is unknown. There are some data indicating that changes in lung parenchyma can occur even at levels of oxygen used for long-term low-flow treatment (1–6 L/min). Petty et al reported evidence of histologic changes consistent with chronic oxygen toxicity in 6 of 12 individuals they studied who had been on oxygen therapy for between 7 and 61 months.<sup>22</sup> Pathology findings consistent with chronic oxygen toxicity included capillary pro-

liferation, interstitial fibrosis, epithelial hyperplasia, and hemorrhage (Fig. 3). The authors found a correlation between the length of oxygen use and pathologic findings consistent with toxicity. There were no control subjects in this series, but the authors noted that in scrutinizing the autopsy findings of 20 case-matched controls who had not received oxygen, they found no cases showing even minor changes consistent with oxygen toxicity. Oxygen use did not appear to contribute to the cause of death in these subjects; in fact, those with the histopathologic changes had no difference in survival compared to those without the changes, when corrected for forced expiratory volume in the first second. The authors reasonably point out that the benefits of oxygen therapy likely far outweigh its potential negative effects. Stewart et al reported finding similar abnormalities in 1 of 5 autopsies they performed in subjects receiving long-term oxygen therapy (LTOT).<sup>23</sup> To date there are no other reports of histopathologic changes from oxygen toxicity in subjects using low-flow oxygen. The overwhelming evidence indicating a survival advantage for those who use low-flow oxygen therapy when it is necessary<sup>24,25</sup> supports the original contention of Petty et al that the benefits of oxygen use in appropriate individuals outweighs the small potential risks of chronic parenchymal oxygen toxicity.

### Mechanism of Oxygen Toxicity

Significant advances in the understanding of oxygen toxicity have occurred in the past several years, and many of the data derive from in vitro cell models. The integration of these laboratory data into a complete explanation of the clinical and pathology findings in humans remains to be accomplished. Current consensus is that tissue oxygen

Table 2. Examples of Factors and Substances That Can Increase or Decrease Sensitivity to Oxygen Toxicity in the Experimental Situation

| Decrease Sensitivity                  | Increase Sensitivity |
|---------------------------------------|----------------------|
| Previous oxygen exposure              | Premature birth      |
| Glutathione                           | Old age              |
| $\alpha$ -tocopherol                  | Hyperthyroidism      |
| Previous lung injury (eg, oleic acid) | Vitamin E deficiency |
| Trace metals (eg, Mg, Zn, Mn, Se)     |                      |
| Hypothermia                           |                      |
| Hypothyroidism                        |                      |

toxicity is related to the excess generation of reactive oxygen species,<sup>26–29</sup> including superoxide anion ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxyl radical ( $OH^\cdot$ ). Reactive oxygen species are chemical intermediates found in many normal cellular reactions within mitochondria, the cytosol, endoplasmic reticulum, and even cell membrane.<sup>29</sup> With normal levels of oxygen as substrate (ie,  $F_{IO_2} = 0.21$ ), toxicity is minimized by the enzymes superoxide dismutase and catalase, which prevent excessive levels of oxygen free radicals.<sup>30</sup> Hyperoxia is thought to lead to excess generation of reactive oxygen species, which overwhelms the capacity of the enzymatic defenses to protect the cell. Excess numbers of reactive oxygen species lead to cellular damage at multiple sites, including cell membrane disruption secondary to lipid peroxidation, inactivation of enzymes due to reduction of sulfhydryl groups, inhibition of deoxyribonucleic acid and ribonucleic acid synthesis, oxidation of pyridine nucleotides, inhibition of glycolytic enzymes, and inactivation of  $Na^+ - K^+$  ATPase.<sup>2,31</sup>

A number of co-factors can increase or decrease hyperoxic pulmonary toxicity (Table 2). Of particular note, intermittent exposure to increased oxygen levels protects against hyperoxic lung injury. Interspersing periods of breathing room air in subjects undergoing hyperbaric oxygen treatment reduces abnormalities associated with oxygen toxicity, such as reduction in vital capacity.<sup>32</sup> The protective effect appears to be related in part to the induction of endogenous protective enzymes such as superoxide dismutase.<sup>33</sup>

#### Adaptive and Maladaptive Physiologic Responses to Low-Flow Oxygen Therapy

Oxygen therapy, even at a low  $F_{IO_2}$ , can result in several normal adaptive physiologic responses. Erythrocyte production mediated through the erythropoietin system is decreased. Pulmonary artery pressure is reduced because of vasodilation in pulmonary vascular bed. Interestingly, the opposite effect (vasoconstriction) occurs in the systemic

vascular bed. However, some of the physiologic responses can be potentially maladaptive, such as hypercarbia.

#### Hypercarbia in Patients with Chronic Obstructive Pulmonary Disease

Elevation of arterial carbon dioxide tension ( $P_{aCO_2}$ ) in COPD patients treated with oxygen has been noted for years and has been attributed to suppression of the hypoxic ventilatory drive.<sup>34,35</sup> The postulated mechanism has been that administration of oxygen eliminates the oxygen drive to breathe in these patients (in whom hypercarbic drive is already blunted by the effects of the COPD), leading to hypoventilation and hypercarbia. However, recent data indicate that a more likely explanation is that supplemental oxygen leads to release of hypoxic vasoconstriction, with change in ventilation-perfusion ratio in the lung, as well as to an exaggerated Haldane effect,<sup>36–38</sup> which leads to hypercarbia. Hypoxic vasoconstriction is a normal physiologic response to hypoxemia. However, in this case, the release of hypoxic vasoconstriction when supplemental oxygen is delivered can lead to an increase in alveolar dead space and, therefore, elevated  $P_{aCO_2}$ . Deoxygenated blood carries more carbon dioxide in the form of bicarbonate than does oxygenated blood. This is known as the Haldane effect. When supplemental oxygen is applied, carbon dioxide carriage and elimination are reduced, resulting in an elevated  $P_{aCO_2}$ . Data are now available to support the latter hypothesis of the elevation of  $P_{aCO_2}$  in response to supplemental oxygen. Studies have shown neither minute ventilation nor central drive to breathe is reduced in either acutely ill<sup>37</sup> or stable COPD patients.<sup>38</sup> Sassoon et al measured transcutaneous carbon dioxide, minute ventilation, mouth occlusion pressure in the first 0.1 second of inspiration, carbon dioxide production, and dead space in 17 subjects with moderate to severe COPD who were blindly exposed to periods of hyperoxia or room air.<sup>38</sup> They found the elevation in measured transcutaneous carbon dioxide was related to changes in dead space, but not to overall minute ventilation or changes in indices of ventilatory drive. Aubier et al noted similar findings in their subjects who were suffering acute exacerbations of COPD.<sup>37</sup> A more recent paper detailing a computer model of the changes of carbon dioxide in response to oxygen in COPD patients indicates that all of the change in  $P_{aCO_2}$  can be explained by the effects of changes in ventilation-perfusion ratio relationships and the Haldane effect, without needing to invoke changes in respiratory drive.<sup>36</sup>

The elevation in  $P_{aCO_2}$  that occurs in response to low-flow oxygen is limited and appears to be reversible if oxygen is discontinued.<sup>23</sup>



Fig. 4. Patient who received second- and third-degree burns caused by smoking while receiving oxygen therapy. (From Reference 41, with permission.)

### Nonmedical Hazards of Long-Term Oxygen Therapy

#### Fire Hazards of Oxygen

Oxygen is not combustible or explosive, but because it supports combustion, the higher the oxygen concentration the greater the rapidity and heat of burning.<sup>39,40</sup> The major fire risks of oxygen therapy are: (1) the increased ease of ignition of the plastic delivery devices used in low-flow therapy and (2) increased flammability of nearby objects such as rugs and drapes because of oxygen leakage from tanks, cryogenic reservoirs, and concentrators.<sup>41</sup>

Significant burns and injury can occur to those who smoke while using low-flow oxygen (Fig. 4). COPD, the most common indication for LTOT, is caused in almost all cases by cigarette smoking. Many patients, including those on LTOT, continue to smoke despite clear evidence of disease caused by smoking. Chemical analysis of the filters of oxygen machines used in the United States indi-

cates that 50% of LTOT patients are in rooms where there is cigarette smoking within 10–15 feet of the machine.<sup>42</sup> Patients must be carefully instructed as to the potential risks of continuing smoking while using LTOT. Despite the danger of fire, relatively few instances of serious injury are reported in the medical literature.

#### Hazards of High-Pressure Oxygen Cylinders

Oxygen for LTOT in the home is sometimes delivered in the form of compressed gas in large metal cylinders at pressures as high as 2,400 pounds per square inch (psi). There are a number of potential hazards associated with their use. Pressure in the tanks can exceed safe levels when ambient temperatures are elevated. Pressure increases 5 psi for every degree above 70° F, and when elevated levels are reached a safety valve opens, releasing oxygen into the surrounding air and creating a fire hazard, if open flames or other sources of extreme heat or combustion are nearby.<sup>41</sup> Tanks must therefore be kept away from open flames and heating devices such as radiators or space heaters. Detonation of tanks can occur if oil or grease comes into contact with oxygen, thus great care must be taken when handling oxygen regulators. Ruptures of gas cylinders have occurred in cases where the cylinder has fallen and dislodged the pressure regulator. The highly pressurized gas evacuating the tank through a small opening can create a heavy metal projectile moving at high velocity. These oxygen "torpedoes" have been seen to penetrate concrete walls and cause serious injury. Therefore, all oxygen cylinders should be properly and securely stored in an upright position.

#### Hazards of Oxygen Concentrators

Oxygen concentrators were introduced for use in home LTOT in 1973.<sup>43</sup> Since that time they have gained wide acceptance. The machinery used in the concentrator is electrically driven; enriched oxygen is in proximity to heat-producing electrical wiring. Few fires have been reported with the use of these devices, despite a large number of manufacturers.

#### Hazards of Liquid Oxygen Delivery Systems

LTOT in the home can be delivered with relatively small, convenient, liquid oxygen systems. Oxygen stored in liquid form at -297° F can be vaporized in a controlled fashion to generate gas-phase oxygen at a low flow rate. The major hazard is related to the very low temperature of the liquid oxygen. The portable carrying devices are well insulated and rarely present a problem, but the process of transferring liquid oxygen from a larger tank into a smaller tank can expose the patient or caregiver to the liquid ox-

xygen or metal that has contacted the liquid oxygen, which can cause burns or even frostbite. Fire is very unusual with liquid oxygen systems, but there has been one report of a delivery truck fire and explosion involving liquid oxygen delivery devices.<sup>44</sup>

### Miscellaneous Effects of Oxygen

Patients using nasal oxygen may experience nasal congestion, irritation of the nasal mucosa, and even epistaxis related to mucosal drying. Allergic reaction to the polyvinyl chloride used in nasal cannulae has been reported and can be treated with topical corticosteroid creams or a change in the brand of cannula.<sup>45</sup> Psychological and social effects of the use of low-flow oxygen therapy outside the hospital have received little attention. Some patients may fear using oxygen because they associate it with the terminal stages of disease.<sup>21</sup> Many patients are self-conscious outside the home when wearing nasal cannula or carrying an oxygen canister. Some patients feel that they may become addicted to the oxygen once they start using it. Careful counseling of the patients and their families may help those patients to become more accepting of and comfortable with a potentially life-prolonging therapy.

### Summary

Exposure to oxygen at a high  $F_{IO_2}$  can result in substantial damage to several organ systems. In contrast, low-flow oxygen is generally quite safe. Although there have been reports of lung tissue injury with low-flow oxygen, the benefits of this therapy in appropriately selected individuals clearly outweighs the small risks. Elevations in  $P_{aCO_2}$  occur in some COPD patients receiving low-flow oxygen and appear to be related to changes in ventilation-perfusion matching in the lung and carbon dioxide transport in the blood stream rather than to reductions in respiratory drive as previously thought. The effect is generally small in magnitude and is not progressive in response to oxygen therapy alone. Nonmedical hazards such as frostbite and fire related to oxygen equipment have been described but are unusual. Minor problems such as skin rash or nasal irritation in those using low-flow oxygen are usually easily handled with topical treatments. Social and psychological problems resulting from a perceived stigma of wearing oxygen may lead to social isolation of the patient and should be addressed with appropriate counseling and education.

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## Discussion

**Petty:** The reason that we published the paper in 1971 is that there was a lot of criticism of the Denver group and its enthusiasm for oxygen, and we were systematically looking for any down side to oxygen.<sup>1</sup> Those lesions may or may not have any clinical relevance at all, as you pointed out. If it was indeed related to oxygen, it occurred in the patients who lived the longest. We were also interested in structure-function relationships in all fresh excised human lungs. That's a whole other story. But, in 1955, as a medical student, after our living on Mount Evans for a month, I wrote an article on the hypoxic threshold,<sup>2</sup> and I got very interested in the hypoxic drive to ventilation, which turns out to be very unimportant normally, but at very high altitude it becomes important. I was taught the year I graduated from medical school in 1958 that you can't give oxygen because of CO<sub>2</sub> retention. And even though I was fascinated by the hypoxic drive, I never believed that that made it impossible to give oxygen to people. And Barach,

the same thing. He controlled low-flow oxygen and found that people could tolerate oxygen very well. Then we published a paper in about 1967 showing that you could correct hypoxemia without getting CO<sub>2</sub> retention in most COPD patients, and this case gave us confidence then to be enthusiastic about going on with oxygen.<sup>3</sup> And, then you get into the CO<sub>2</sub> retention thing. That does occur, of course, as the disease progresses, but very likely chronic compensated CO<sub>2</sub> retention is adaptive to high work of breathing. And, again, that was an idea of Barach, because if you can adjust your P<sub>CO<sub>2</sub></sub> to, say, 80, and generate appropriate bicarbonate to balance the pH scales, then it's very efficient to have your P<sub>CO<sub>2</sub></sub> at 80, because a lower level of minute ventilation maintains CO<sub>2</sub> homeostasis. The late Tom Neff and I published an article called "Tolerance and Survival in Severe Chronic Hypercapnia."<sup>4</sup> We published on a large number of patients who were living at home where the mean P<sub>CO<sub>2</sub></sub> was over 90. A lot of these people could function, including driving a truck. We published a picture of a road inspector

who was driving a truck with a P<sub>CO<sub>2</sub></sub> of 94 and a pH of 7.35. So, CO<sub>2</sub> actually can be good for you, and is not necessarily deleterious.

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**MacIntyre:** Josh, that was a great talk. I have a comment and then a question. The comment: Back in my younger days I was a Navy flight surgeon. We published a study on military pilots who routinely would expose themselves to 100% O<sub>2</sub> because of their job of flying a jet fighter plane.

Over a career, these guys would have over 5,000 hours of exposure to 100% oxygen. We did pulmonary function tests on them and compared them to helicopter pilots who were not exposed to 100% oxygen, but who had similar amounts of flying time, and found no real difference. So, intermittent exposure to 100% oxygen for 5,000 hours total dose doesn't seem to do much to your lungs. Now the question: I understand the fact that hypoventilation doesn't seem to be important in most cases of chronic CO<sub>2</sub> retention. But there are cases of patients in the emergency room or being transported in ambulances, where someone slaps an oxygen mask on a CO<sub>2</sub> retainer and, lo and behold, they do have a respiratory arrest. What is the mechanism of that?

**Benditt:** I'm not sure what the mechanism of that is, but I think there is contribution of central nervous system depression in terms of drive. Actually, in Aubier's paper,<sup>1</sup> patients had very significant elevations in CO<sub>2</sub> that could not be explained by the ventilation-perfusion matching argument alone. So I think there clearly is that. What it is about those patients that's different, I don't know, whether it's central drive or what. But, I agree. Clearly that exists. I think the changes with the Haldane effect and the ventilation-perfusion matching can occur very quickly, but I agree it doesn't explain everything in the really severe patients. I would say the intermittent exposure to oxygen—I think it's crucial and might explain your data—that is it is very clear from a lot of experiments that if you give it, then take it away, give it, then take it away, they will become much more tolerant to the changes in vital capacity. That's very interesting. People have said "Well, it's induction of the *superoxide* dismutase enzymes, and they can handle the oxygen now," but no one has ever really proven that.

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**Stoller:** Neil, I too have wondered about that heterogeneity of hypercapnic response, and I think, in recalling Aubier's paper, there was a temporal relationship between minute ventilation and the exposure, such that initially there was actually a more impressive drop in minute ventilation than was observed at 15 minutes. There were those 2 patients you pointed out who had an impressive hypercapnic response, and perhaps what we're seeing in the ambulance is the pronounced example of someone whose acute minute ventilatory drop in response to supplemental oxygen is more pronounced. I don't pretend to understand what segregates those 2 populations, but I think it's more complicated than simply the one or the other. And, in fact, most of these articles try to project how much contribution can be explained by the ventilatory response (ie, alveolar hypoventilation), how much can be explained by the Haldane effect, and how much can be explained by ventilation-perfusion mismatch. In fact, it's probably true that all 3 are playing contributing roles to varying degrees.

**O'Donohue:** I think there's a real difference between those patients who are in acute respiratory failure with hypercapnia and those patients with chronic hypercapnia who are receiving oxygen therapy. Patients in acute respiratory failure are usually severely fatigued, and they have many other medical problems. It's almost predictable that if you give them too much oxygen and they're hypercapnic, you're going to get further ventilatory depression, or you're going to see a

significant increase in P<sub>CO<sub>2</sub></sub> and a decrease in pH.

**Pierson:** This is similar to the discussion we had after my presentation about what's actually going on—whether it's ventilation-perfusion or shunt or what. I think we need to make the distinction between the physiological particulars and the clinician's observations, and what one needs to know to manage patients. I have been reprimanded for oversimplifying this effect in acutely ill COPD patients—that is, if you give them too much oxygen, things may not go well—and ascribing that more to drive changes than I should have, but the fact remains that if you give that patient too much oxygen, things won't go well, so that we may discuss the actual mechanisms, but, again, the clinical advice seems sound that excessive oxygenation in acute exacerbations can sometimes get you into trouble.

**Hess:** Could I put a little bit different twist on the Haldane effect? In the intensive care unit, you're taking care of an acute respiratory distress syndrome (ARDS) patient whom you're having difficulty oxygenating and ventilating, and the team is trying to keep the oxygen saturation (to use your example) at 95%. Could you improve not only the risk of oxygen toxicity by reducing the fraction of inspired oxygen (F<sub>IO<sub>2</sub></sub>), but also lowering the oxygen saturation to improve the arterial P<sub>CO<sub>2</sub></sub> due to the Haldane effect?

**Benditt:** Right.

**Hess:** A question that I would say a house officer asked me not too long ago. Left me scratching my head, so. . .

**Benditt:** That's a good question.

**Hess:** I thought that was an interesting twist on the Haldane effect.

**MacIntyre:** So, you're trading a metabolic acidosis for a respiratory acidosis, or vice versa?

**Hess:** Well, this is your ARDS patient with a  $P_{CO_2}$  of 60. Can you lower the arterial  $P_{CO_2}$  by lowering the oxygen saturation, making more room on the hemoglobin to bind  $CO_2$  and thus lower the arterial  $P_{CO_2}$ ? Sort of the reverse of what you were talking about.

**Benditt:** Well, I guess it depends on the magnitude of the effect, and I think we have actually underestimated the Haldane effect, from what I have read from the advanced physiologists talking about this. But I don't know what the difference would be between 95% and 89% or 90%.

**Hess:** Because what you were talking about during your talk is that you raise the oxygen saturation so as the  $P_{CO_2}$  goes up. So what about the reverse of that?

**Benditt:** I would agree, that's certainly possible.

**Bradley:**\* I have a question. I know there was some discussion about increased depression scores for patients who were initiated on long-term oxygen therapy. In your practice, do you feel that this is more from decrease in the ability to freely ambulate, or do you feel that it is due to the idea that they succumb to their disease process to the point where they're on continuous oxygen therapy?

**Benditt:** Probably Dr Petty can answer that better than I, but what I would say is that I think they can ambulate farther with the oxygen. Many people, including Jerry Criner, have shown that COPD patients can exer-

cise farther with oxygen.<sup>1</sup> I think there is something psychological about having nasal cannulae, in particular, that affects these patients. Again, with lung reduction, people come in saying they want this operation because "I want not to wear oxygen." Sometimes it's to the point where they'll not wear it when they should wear it, for whatever reason. So, I think it has something to do with the symbolic nature of this thing. Because I think they can do more. I think they're less dyspneic but it's something psychological. Dr Petty probably has the most experience with that.

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**Petty:** Transtracheal oxygen delivery is a good example of a way to make the use of oxygen more tolerable. Even though it's argued that it's more than cosmetic. Transtracheal oxygen really is a conserving technique, and it also participates in a little bit of conductive acceleration. I think the main thing that transtracheal does is it makes oxygen more palatable to the patient. And I already made mention that I've seen people that I think were made a lot worse once prescribed oxygen, because they equated it with imminent death and suffered severe depression. I've seen specific patients with this.

**Wedzicha:** Can I take issue with you about this problem about nasal cannulae? Certainly, what I find in the UK is that although I give patients their little oxygen cylinders, patients actually don't want to use the oxygen outside the home; it's being seen with oxygen that is the issue, I think, not the nasal cannula. And, again, sometimes we use facial masks. I certainly

wouldn't say that transtracheal oxygen therapy is the answer to nasal cannulae. Indeed, transtracheal oxygen therapy has a lot of morbidity associated with it, and I think some of our early and physiological advantages of it really haven't been proven.

**Benditt:** Let me say first of all that I absolutely agree. Lung volume reduction surgery is not the answer to hypoxemia. All I guess I'm saying is that in the past 3 or 4 years, as part of this program, I've seen probably 300 patients with very severe COPD, and a really recurring theme with them is the oxygen use. I guess I don't know whether it's actually the cannula or the canister, or what. But it has some meaning for them that is nonphysiologic, because I think they are doing better with the oxygen. They're certainly living longer, and I think they're exercising more. But there is something about it. Jerry, you've worked with a lot of these patients. It's really a common theme that what they want to do from this procedure is get rid of the oxygen therapy. Now that does not happen in many patients. So, I would agree with you. I would never recommend it for that.

**Criner:** Most patients, I'd say almost 95% of patients that we see, despite being prescribed oxygen for years by pulmonologists, don't know why they're using the oxygen, other than their doctor told them to use it. I think once they have been instructed as to why they're using it, what the effects of oxygen are on their survival and other physiologic functions, most of the patients are much more accepting of the use of oxygen. In our experience with lung volume reduction surgery, we tell our patients that they're probably going to need more oxygen when they exercise. Most of them do require more oxygen and are much more accepting of oxygen use coupled with an improvement in their

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physiologic status. I think a lot of the patient's tolerance to oxygen reflects on what education, teaching, and expectations the patients have of why they're using it.

**Spratt:\*** I agree wholeheartedly with Gerry's comments. As a provider, a problem that we deal with is trying to get our patients to wear their oxygen. Most of our problems, quite honestly, are clinician-induced. Most of what we fight against is misinformation from physicians, nurses, therapists. Certainly well-meaning, they want to keep you off oxygen as much as they possibly can, and that's still very prevalent out there. If we have a physician such as yourself who does a great education job, our job is generally very easy. If we have a physician telling them the opposite, as is often the case, our job is very difficult. I think we are making some strides there, and I don't have a clinical study, but I'll call it the "Wal-Mart study" in that I see a lot more patients out in public now who are using their O<sub>2</sub> therapy than I did, say, 15 years ago, certainly when I entered the field, and I think it's getting better all the time as the education is getting better. But we still have a huge gap where we don't have physicians, nurses, therapists who, even in their own minds, are clear on why we use oxygen therapy and the benefits.

**Kacmarek:** I believe that the aversion patients have is the way you and

I and everybody else in society looks at them when they are receiving oxygen. They are announcing to the world that they are sick. It's quite obvious to everybody that they are sick, and people act and treat them differently. To me, this is the biggest issue that patients have regarding LTOT—the reactions they get from others around them when they're seen with O<sub>2</sub>. I believe most of us would do the same thing. It's probably a similar reaction we would get if we were orthopedic surgeons sitting here talking about patients with crutches or prostheses where it is obvious to the world that there is something wrong with them. I'm not sure that you can ever fix this. This is a common attitude that we have as humans develop about being different from everybody else.

**McCoy:** I've got a comment about that. I think we're at a turning point right now. We're talking about history, and things are changing in long-term oxygen therapy on a daily basis. We now have 5-pound portables that are packaged in fanny packs that are very well hidden. The cannula is still noticeable, but it's becoming more practical, easier for patients to ambulate. The point about patients being seen, I see some very snazzy wheelchairs out there, patients who are in a candy apple red wheelchair tooling around just like they do in their car, gaining attention. But, it's not necessarily negative attention. I think that as we package oxygen therapy products in more fashionable packages, it may become a fashion statement that you have a red cylinder and I have a

blue cylinder to go with my outfit. It's at the turning point right now.

**Kacmarek:** You're making my argument. The less you look different, the more you'll be accepted. Why the patient with transtracheal feels better, no one knows. If they have a transtracheal catheter, they can hide it; no one is aware of the fact they're receiving O<sub>2</sub>. The more we can make LTOT cosmetically acceptable, the less people will be adverse to using it.

**Stoller:** At the risk of maybe being simplistic, I guess I think of the whole issue of counseling patients with supplemental oxygen is kind of a host-environment problem, which perhaps synthesizes the comments we've heard. The environment is hostile to the use of supplemental oxygen because of social stigmata. I think Dr Criner's point is that our job as physicians in interfacing with patients is to remind them of the offsetting benefits (in the context of a hostile environment) that allows acceptance, and, in fact, embraces the technology and a therapy that enhances the caliber and longevity of their lives. In instances where we are unsuccessful, as Dr Petty so nicely pointed out, in overcoming that personal aversion, it's perhaps best not to prescribe oxygen despite its physiologic benefits. I think we have to see all these issues of counseling in the social context of the therapy. This is a paradigm that we face with every therapy, whether it's a pill, or inhaler, or supplemental oxygen, or chronic ventilation, or wheelchairs, or whatever it may be.

\*Greg Spratt, Rotech Medical Corporation, Kirksville, Missouri.

# Detection and Monitoring of Hypoxemia and Oxygen Therapy

Dean Hess PhD RRT FAARC

## Introduction

### Clinical Signs of Hypoxia and Hypoxemia

#### Arterial Blood Gases

#### Arterialized Capillary Blood Gases

#### Point-of-Care Testing

#### Blood Gas Monitors

#### Pulse Oximetry

#### Transcutaneous Partial Pressure of Oxygen

#### Mixed Venous Blood Gases

#### Venous Oximetry

#### Gastric Tonometry

#### Monitoring in Perspective

#### Recommendations for Oxygen Monitoring in Various Clinical Settings

## Summary

[Respir Care 2000;45(1):65–80] *Key words: arterial blood gas, capillary blood gas, point-of-care testing, blood gas monitor, pulse oximetry, transcutaneous blood gas, mixed venous blood gas, venous oximetry, gastric tonometry.*

## Introduction

The deleterious effects of hypoxia are familiar to all clinicians. Thus, it is not surprising that many technologies have been developed to measure and monitor oxygenation. Some of these have become ubiquitous in the past 10 years (eg, pulse oximetry). Devices to evaluate oxygenation can be categorized in several ways (Fig. 1). These devices may be invasive or noninvasive, continuous or intermittent.<sup>1</sup> They can be used to evaluate arterial oxygenation, venous oxygenation, oxygen delivery, oxygen uptake, or a combination of these.

### Clinical Signs of Hypoxia and Hypoxemia

The clinical signs of hypoxia and hypoxemia are well known to most clinicians (Table 1). Unfortunately, these

clinical signs are neither sensitive nor specific. A high index of suspicion in conjunction with the presence of clinical signs suggestive of hypoxemia may prompt quantitative assessment of oxygenation. However, interobserver reliability of the clinical signs of hypoxemia falls between chance and total agreement, and is relatively independent of the experience of the observer.<sup>2</sup>

Cyanosis is a clinical sign often associated with hypoxemia, but, for a number of reasons, cyanosis can be unreliable as a clinical sign.<sup>2</sup> Cyanosis will not be present until oxygen saturation decreases to < 85%, it will be absent despite severe hypoxemia in the presence of anemia, or it will be exaggerated in the presence of polycythemia. Cyanosis can be difficult to detect in poor lighting. Cyanosis can occur with methemoglobinemia or sulfhemoglobinemia, conditions in which cardiopulmonary function and arterial partial pressure of oxygen ( $P_{aO_2}$ ) may be normal. Central cyanosis is usually attributed to lung disease, whereas peripheral cyanosis is attributed to cardiovascular disease.

### Arterial Blood Gases

Arterial blood gas (ABG) analysis is the indisputable gold standard for evaluation of arterial oxygenation. Elec-

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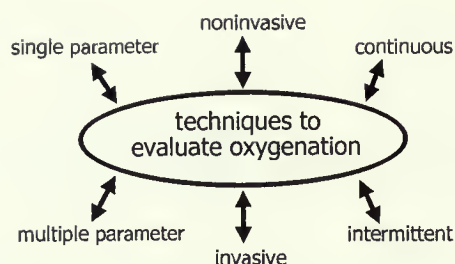


Fig. 1. Evaluation of oxygenation can be invasive or noninvasive, continuous or intermittent, single parameter or multiple parameter.

trochemical (electrode) techniques to measure the partial pressure of oxygen ( $P_{O_2}$ ) in whole blood were introduced by Dr Leland Clark in the mid-1950s.<sup>3</sup> Although guidelines for ABGs have been published,<sup>4</sup> the indications for this analysis remain somewhat unclear.<sup>5</sup> Indications for ABGs listed in the American Association for Respiratory Care Clinical Practice Guidelines are: the need to evaluate the adequacy of ventilation (arterial partial pressure of carbon dioxide [ $P_{aCO_2}$ ]), acid-base levels (pH and  $P_{aCO_2}$ ), oxygenation ( $P_{aO_2}$ , arterial oxygen saturation [ $S_{aO_2}$ ]), and oxygen-carrying capacity of the blood ( $P_{aO_2}$ , hemoglobin oxygen saturation [ $O_2Hb$ ]), hemoglobin [Hb], and dyshemoglobins); the need to quantitate the patient's response to a therapeutic intervention or diagnostic evaluation; and the need to monitor severity and progression of a documented disease process. It is important to recognize that  $P_{aO_2}$  is primarily the result of lung function, and may have no relationship to oxygen delivery to tissues or tissue oxygenation. There are numerous problems associated with the measurement and use of ABGs (Table 2), and these are generally well known.<sup>1</sup>

Laboratory evaluation accounts for about 25% of total critical care costs, and ABGs are the most frequently ordered laboratory test in critical care units. A rate of 4.8 ABGs per patient per day was reported from a surgical intensive care unit (ICU).<sup>6</sup> The presence of an arterial line was the single most powerful predictor of the number of blood gases drawn per patient. This occurred regardless of the values for  $P_{aO_2}$ ,  $P_{aCO_2}$ , Acute Physiology and Chronic

Table 1. Clinical Signs of Hypoxemia

|                                                  |
|--------------------------------------------------|
| Cyanosis                                         |
| Restlessness, disorientation, lethargy, and coma |
| Tachypnea                                        |
| Dyspnea                                          |
| Hyperpnea                                        |
| Tachycardia or bradycardia                       |
| Arrhythmias                                      |
| Hypertension or hypotension                      |
| Polycythemia                                     |
| Clubbing                                         |

Table 2. Problems Associated with Arterial Blood Gas Analysis

|                                                                                                     |
|-----------------------------------------------------------------------------------------------------|
| Pain                                                                                                |
| Preamalytical errors: air contamination, heparin dilution, storage, excessive delay before analysis |
| Analytic errors: accuracy differences between models of blood gas analyzers                         |
| Postanalytical errors: transcription errors, delays in reporting results                            |
| Infection risk to patient (particularly with arterial catheter)                                     |
| Infection risk to clinician (particularly with arterial puncture)                                   |
| Thrombosis and distal embolization (particularly with arterial catheter)                            |
| Blood loss (particularly with arterial catheter)                                                    |
| Intermittent information                                                                            |
| Cost                                                                                                |
| Regulation: Clinical Laboratory Improvement Amendments of 1988 (CLIA-88)                            |

Health Evaluation (APACHE) II score, use of ventilators, or use of pulse oximeters. The presence of an arterial line also affects the pattern of transfusion requirements related to phlebotomy for diagnostic tests in adults.<sup>7-9</sup> Although excessive phlebotomy for diagnostic testing is well appreciated in neonates, this can also be a problem in adults. In one report, patients with an arterial line were phlebotomized at a rate twice that of patients who did not have an arterial line.<sup>7</sup> Another study reported increases in the number of blood tests (29% increase), blood-drawing procedures (30% increase), and the amount of blood volume loss (44% increase) from patients with arterial lines, compared to those without.<sup>8</sup>

Several strategies might be used to decrease the blood loss from ABGs (and other laboratory testing) in critically ill patients.<sup>10</sup> The routine use of arterial lines can be avoided. Blood conservation systems can be used to eliminate the discard volume from arterial line blood draws.<sup>11-15</sup> Multiple diagnostic tests can be performed on a single sample of blood. Clinically accurate and precise invasive and noninvasive technology might be able to be substituted for some diagnostic tests. Blood sample volume can be reduced, such as by using pediatric phlebotomy tubes with smaller syringe volumes.<sup>13</sup> Third, and perhaps most important, guidelines can be used to improve the appropriateness of diagnostic testing.

The benefit of guidelines and protocols for obtaining ABGs has been reported by several groups of investigators. Beasley et al established procedural, clinical, and therapeutic indicators for ABGs in a surgical ICU.<sup>16</sup> A forced interaction between respiratory therapists and nurses was established by having therapists responsible for ABG analysis, which resulted in a significant improvement in the appropriateness of ABGs obtained by the nurses. Pilon et al<sup>17</sup> developed institutional guidelines for blood gas measurement in a tertiary teaching hospital, and reported an approximately 50% decrease in the number of ABGs, with near doubling of appropriateness. It is important to

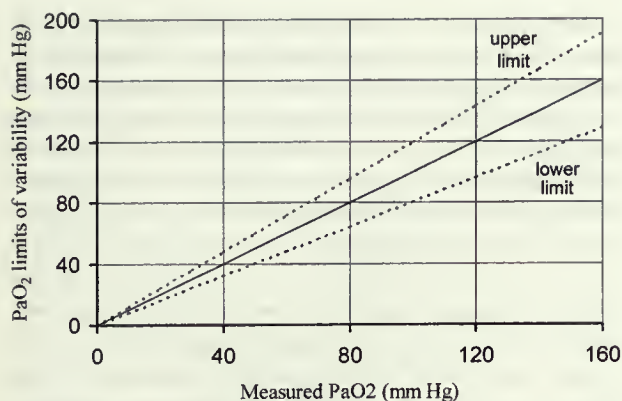


Fig. 2. Limits of spontaneous variability of arterial partial pressure of oxygen ( $P_{aO_2}$ ) in stable, mechanically ventilated trauma patients who were not disturbed during the evaluation period. (Adapted from Reference 18.).

develop a behavior among respiratory therapists, physicians, and nurses that carefully considers the need for blood gas analysis: there is little or no need for routine blood gas analysis (eg, after each ventilator change).

One frequently unappreciated feature of intermittent ABG analysis is spontaneous variability (ie, changes in blood gas levels without any intervention or interaction with the patient).<sup>18–21</sup> In a study of stable, mechanically-ventilated trauma patients who were not disturbed during the study period, the coefficient of variation in  $P_{aO_2}$  between 4 ABGs drawn at 20-minute intervals was  $5.1 \pm 3.2\%$ , median 3.6%, 95th percentile 9.8%.<sup>18</sup> The clinical importance of this is illustrated in Figure 2. Changes in  $P_{aO_2}$  within the limits of spontaneous variability and without an associated clinical change might be the result of spontaneous variability.

An important clinical issue relates to the amount of time required to establish a new steady state after changing the level of oxygen provided to the patient. If too little time is allowed, the blood gas results will not reflect the new clinical conditions. On the other hand, too much time could subject the patient to a period of potentially harmful hypoxemia. The time required to reach a steady state after changing the fraction of inspired oxygen ( $F_{IO_2}$ ) depends on the alveolar ventilation and the functional residual capacity. A lower alveolar ventilation or a larger functional residual capacity requires a longer time for equilibration. Unless the patient has obstructive lung disease (which results in a lower alveolar ventilation and a larger functional residual capacity), 5 minutes is usually adequate time to reach a new steady state after changing the  $F_{IO_2}$ .<sup>22</sup> For patients with obstructive lung disease, 30 minutes should be allowed to reach a new steady state after changing  $F_{IO_2}$ .

The accepted standard for measurement of  $O_2Hb$  is CO-oximetry,<sup>23</sup> which uses multi-wavelength spectrophotom-

etry to measure  $O_2Hb$ , deoxyhemoglobin (HHb), carboxyhemoglobin (COHb), and methemoglobin (metHb). Fractional oxyhemoglobin ( $FO_2Hb$ ) is then calculated as:

$$FO_2Hb = (O_2Hb)/(O_2Hb + HHb + metHb + COHb)$$

An alternative method is to calculate hemoglobin oxygen saturation (functional saturation):

$$SO_2 = (O_2Hb)/(O_2Hb + HHb)$$

This method is discouraged because it overlooks the effects of dyshemoglobins and thus overestimates the true oxygen saturation.  $SO_2$  can also be calculated from the measured  $P_{O_2}$  using an empirical equation for the oxyhemoglobin dissociation curve; this is commonly done using software in blood gas analyzers. Clinically important errors can result from use of a calculated  $SO_2$  in applications such as the shunt equation.<sup>24–27</sup> It should never be assumed that  $FO_2$ ,  $SO_2$ , and calculated  $SO_2$  are equivalent.

There are several potential errors related to CO-oximetry. Because of differences in the light absorption spectra of fetal hemoglobin (HbF) and adult hemoglobins, the presence of HbF may result in a falsely elevated COHb reading.<sup>28</sup> Correction factors for the presence of HbF have been published,<sup>29</sup> but these may not be appropriate under all conditions (eg, transfusion).<sup>30</sup> Intralipid infusions<sup>31</sup> and propofol infusions may result in a falsely elevated metHb reading measured by CO-oximetry.

### Arterialized Capillary Blood Gases

Capillary blood gas samples have been used in place of arterial puncture. A puncture is made with a lancet or similar device into the cutaneous layer of the skin at a highly vascularized area. To accelerate blood flow and reduce the difference between arterial and venous gas pressures, vasodilation is achieved by warming or use of a vasoactive cream. Common sites used for collection of arterialized capillary blood gas samples are the heel (in neonates), finger, toe, or earlobe.<sup>32</sup>

Although used more commonly in neonatal and pediatric patients, several recent studies have reported the use of arterialized capillary blood gas measurement in adults. Pitkin et al reported good agreement between capillary  $P_{O_2}$  and arterial  $P_{O_2}$  (bias  $-1$  mm Hg, limits of agreement  $-8$  mm Hg to 6 mm Hg).<sup>33</sup> Dar et al reported "trivial and nonsignificant" differences between arterial and capillary  $P_{O_2}$ .<sup>34</sup> In contrast, Sauty et al<sup>35</sup> reported a significant underestimation (4 mm Hg) of  $P_{aO_2}$  by earlobe capillary blood gases, with wide limits of agreement ( $-4$  mm Hg to 13 mm Hg).

Arterialized capillary blood samples contain a mixture of blood from capillaries and venules.<sup>36</sup> Normally, the

difference between arterial and venous  $P_{O_2}$  is large (about 60 mm Hg), but this difference can be reduced by vasodilation. Furthermore, the difference between arterial and venous  $P_{O_2}$  decreases with hypoxemia. Thus, the accuracy of arterialized capillary blood  $P_{O_2}$  measurement improves as the  $P_{aO_2}$  decreases. Nonetheless, arterialized capillary  $P_{O_2}$  systematically underestimates the  $P_{aO_2}$ . It is interesting to note that capillary blood samples are difficult to obtain anaerobically. Exposure of the blood to room air raises the  $P_{O_2}$  and this pre-analytic error may explain the agreement between arterialized capillary  $P_{O_2}$  and  $P_{aO_2}$  reported in some studies. The potential for poor agreement between arterialized capillary  $P_{O_2}$  and arterial  $P_{O_2}$  and the potential for room air contamination of the sample significantly reduces the usefulness of this technique.

The use of arterialized capillary blood gas measurement has been advocated as a method that can be used by non-physicians.<sup>36</sup> However, arterial punctures are commonly and safely performed by respiratory therapists. Arterialized capillary blood gases have also been advocated because they are less painful.<sup>34</sup> Although arterial puncture can be painful, the pain can be ameliorated by the use of local anesthesia.<sup>37</sup>

### Point-of-Care Testing

Samples for blood gas analysis are drawn, prepared, packaged, transported to the laboratory, analyzed, and the results are then communicated back to the patient care unit.<sup>38–42</sup> This system can result in pre-analytical errors (eg, failure to properly transport the sample), postanalytical errors (eg, transcription errors in reporting the results), and considerable delay in obtaining test results. There has been increasing interest in point-of-care (POC) testing, in which blood gases are measured at or near the site of patient care.

POC testing has been shown to be accurate and useful despite concerns regarding regulatory, managerial, quality, and turf issues.<sup>40</sup> Several studies have reported acceptably accurate blood gas results using POC testing devices.<sup>43–50</sup> Studies of modern POC blood gas analyzers<sup>46–49</sup> indicate that in this class of instruments  $P_{O_2}$  bias  $\pm$  precision ranges from  $-2 \pm 11$  mm Hg to  $5 \pm 20$  mm Hg,  $P_{CO_2}$  bias  $\pm$  precision ranges from  $-1.3 \pm 2.0$  mm Hg to  $1.6 \pm 1.4$  mm Hg, and pH bias  $\pm$  precision ranges from  $-0.010 \pm 0.017$  to  $0.02 \pm 0.04$ . Kendall et al<sup>51</sup> performed a randomized, controlled study of POC testing and clinical outcome in an emergency department. They reported that POC testing resulted in significantly faster decision-making; for example, ABG results were obtained 21 minutes earlier. However, POC testing did not affect the amount of time spent in the emergency department, length of hospital stay, admission rates, or mortality.

There are currently more than 10 manufacturers of POC testing devices that measure blood gases.<sup>38</sup> Desirable features of POC testing devices have been recommended (Table 3). POC testing devices are portable and some are hand-held. They typically require a small volume of blood (a few drops) for testing. Blood is introduced into a single-use disposable cartridge that is introduced into the portable analyzer. The cartridge chosen determines the tests that will be run (eg, blood gases, electrolytes, hematocrit, glucose, blood urea nitrogen, creatinine, ionized calcium, and others). A calibrating solution automatically calibrates the sensor, after which the blood sample is drawn over the biosensors. The POC analyzer then calculates, displays, and stores the results. The POC testing device can communicate with the central laboratory or hospital information system for reporting and archiving results.

The role of POC testing is evolving and will continue to expand. Two issues that must be addressed before more widespread use are regulation and cost. Quality control and quality assurance must also be appropriately addressed, which is typically achieved by following the manufacturer's recommendations for use of the device. Cost is more difficult to address.<sup>51,52</sup> Currently the cost of the basic unit is about \$3,000 and the cost of the single-use cartridges is about \$5 (i-Stat monitor [i-STAT Corporation, Princeton, New Jersey]). However, this cost must be balanced against quicker test turnaround time (potentially resulting in more rapid treatment and better patient outcome), lower overhead (compared to the central laboratory), and the smaller blood volume required for testing (resulting in lower transfusion requirements).

### Blood Gas Monitors

There has been considerable interest in the critical care community for a system to monitor ABGs and pH.<sup>42,53–58</sup> Several manufacturers have United States Food and Drug Administration approval for such systems. Blood gas monitors measure pH, partial pressure of carbon dioxide ( $P_{CO_2}$ ), and  $P_{O_2}$  without permanently removing blood from the patient.

Current-generation blood gas monitors use fluorescent optical biosensors called "optodes," first developed by Lübbers and Opitz, who coined the word "optode."<sup>59,60</sup> A light source activates electrons in the dye to a higher energy state. When the light exposure ends, the electrons return to their basal state, and light is re-emitted. The lower-frequency re-emitted light is augmented as the concentration of hydrogen ion or carbon dioxide increases, or is quenched as the concentration of oxygen increases. Photosensors are used to quantify the amount of quenching, and a microprocessor is used to translate the signal into a display of the  $P_{O_2}$ ,  $P_{CO_2}$ , and pH readings. Various configurations of optodes for intra-ABG monitors have been developed. Op-

tode systems are electrically isolated from the patient, they can be miniaturized so that they fit through a 20-gauge arterial catheter without affecting blood pressure measurements or other catheter functions, they are stable over time, they respond rapidly to changes in substrate concentration, and they are not consumed in the measurement process.<sup>53-55</sup> Shapiro<sup>53</sup> has suggested minimal requirements for a blood gas monitor in conjunction with an arterial catheter (Table 4).

Several approaches can be taken to blood gas monitoring in conjunction with an arterial catheter.<sup>53-55</sup> The first approach uses a probe that passes through the arterial catheter and resides directly within the arterial lumen (ie, in vivo blood gas monitor). With the second approach, the optode system is connected to the proximal arterial line, but does not pass through the catheter. With this method, when a measurement is desired, blood is drawn into a chamber containing the optodes (ie, ex vivo blood gas monitor), and after analysis the blood is flushed back into the artery. Thus, frequent (but *not* continuous) blood gas measurements are possible without blood loss.

A number of studies evaluating these devices have been reported in the peer-reviewed literature.<sup>61-76</sup> In vivo and ex vivo blood gas monitors have been evaluated in adults, children, and neonates. Studies of blood gas monitors<sup>42,53,55,61-76</sup> indicate that in this class of instruments  $P_{O_2}$  bias  $\pm$  precision ranges from  $-6 \pm 13$  mm Hg to  $5 \pm 17$  mm Hg,  $P_{CO_2}$  bias  $\pm$  precision ranges from  $-3.0 \pm 4$  mm Hg to  $4.5 \pm 6$  mm Hg, and pH bias  $\pm$  precision ranges from  $-0.04 \pm 0.03$  to  $0.013 \pm 0.031$ . It is troublesome, however, that some of these studies report occasional discrepancies between the blood gas monitor and a blood gas analyzer. The reasons for this are not clear but may relate to issues such as sensor position and catheter flushing.

Two considerations are important when evaluating the accuracy of these devices. First, although the accepted standard for comparison is ABG, *laboratory accuracy* should be separated from *clinically-useful accuracy*. It is conceivable that a device that does not meet laboratory accuracy standards might still be a useful clinical evaluation device in the ICU. Second, although in vivo blood gas monitoring devices may (or may not) sacrifice some of the accuracy of the blood gas analyzer, in vivo devices are not subject to the preanalytical errors that occur with ABGs.

Despite considerable clinical interest, the future of in vivo blood gas and pH measurement is unclear. One problem with these systems is cost (\$20,000 for the monitor and \$300 for the sensor). Although blood gas analyzers are equally expensive, they are not dedicated to a single patient. Although manufacturers are striving to design easy-to-use systems, the amount of technical attention these systems are likely to require in a busy ICU remains to be determined. The life of the sensor and its effect on the function of the arterial catheter system (eg, blood pressure

measurements) also remain to be seen. The quality-control and quality-assurance requirements for clinical and regulatory purposes are currently unclear. There will also probably be interest in using these systems to achieve closed-loop ventilation. To avoid mistakes made with pulse oximetry, the effect of these systems on outcome needs to be evaluated. Whether the benefits of continuous blood gas and pH measurements will outweigh the costs and technical support required remains to be seen.

### Pulse Oximetry

Pulse oximetry, a technology unavailable until the mid-1980s, is now commonly used throughout the world. Pulse oximeters can be used in prehospital care, in emergency medicine, for monitoring the fetus during labor and delivery, in acute care, in extended care facilities, and in home care. With virtually no scientific evaluation of its impact on outcome, continuous pulse oximetry has become a standard of care for critically ill patients. Pulse oximeters are available as small hand-held units, as semi-portable units with alarms and waveform display, in combination with other monitors such as those for capnography and transcutaneous partial pressure of carbon dioxide ( $P_{tcCO_2}$ ), incorporated into mechanical ventilator systems, and as part of the bedside critical care monitoring system.

The technical and physiologic aspects of pulse oximetry have been reviewed in detail elsewhere.<sup>77-87</sup> Two wavelengths of light (660 nm and 940 nm) from two light-emitting diodes (LEDs) are passed through a pulsating vascular bed and transmitted light is measured by a photodetector. Although reasonably specific, there is some error in the wavelength of light emitted by the LEDs ( $\pm 30$  nm), which can affect accuracy. Also, the photodetector is not specific (ie, it will respond to any wavelength of light, which can result in interference). Although some of the light emitted from the LEDs is absorbed by each constituent of the tissue, the only variable absorption is due to arterial pulsations. This is translated into a plethysmographic waveform. The ratio of the amplitudes of these

Table 3. Desirable Characteristics of Point-of-Care Testing Devices

|                                                                                      |
|--------------------------------------------------------------------------------------|
| Ability to trace and describe errors                                                 |
| Management and quality control and quality assurance to meet regulatory requirements |
| Easy to calibrate                                                                    |
| Ability to download information to hospital information system                       |
| Long shelf life for cartridges and reagents                                          |
| Ability to modify and update tests that can be done                                  |
| Vendor support and reliability                                                       |
| FDA approval                                                                         |

Adapted from Reference 38.

two plethysmographic waveforms is translated into a display of oxygen saturation.

A probe is used to pass light from the LEDs through a pulsating vascular bed. Disposable and reusable probes are available and equally accurate.<sup>88</sup> Although most pulse oximeters use transmission oximetry (ie, the light from the LEDs is transmitted through the tissue and the photodetector is opposite the LEDs), some designs use reflectance oximetry (ie, the light from the LEDs is reflected from the tissue and the photodetector is on the same side of the tissue as the LEDs). To obtain valid data, manufacturers' instructions must be followed regarding proper placement of the probe. Pulse oximetry probes can become contaminated with pathogenic bacteria<sup>88</sup> and thus be as a source of nosocomial infection. A protective sheath can be used to allow the same disposable probe to be used on multiple patients.<sup>89,90</sup> The use of disposable pulse oximetry probes can become very expensive for the hospital, and it has been shown that disposable pulse oximetry probes can be gas-sterilized and recycled.<sup>91</sup> Programs are available from some manufacturers for recycling of disposable pulse oximetry probes.

The limitations of pulse oximetry should be recognized, appreciated, and understood by everyone who uses pulse oximetry data.<sup>92-95</sup> Most pulse oximetry errors can be explained as too little signal (eg, low perfusion, improper probe placement) or too much noise (eg, motion, ambient light).

### Accuracy

Pulse oximeters use empirical calibration curves developed from studies of healthy volunteers. Many clinical evaluations of the accuracy of pulse oximeters have been

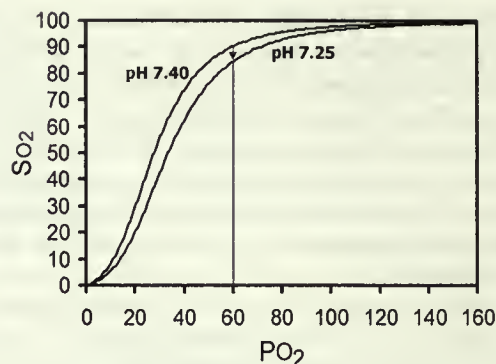


Fig. 3. Oxyhemoglobin (HbO<sub>2</sub>) dissociation curve, relating oxygen saturation (S<sub>O<sub>2</sub></sub>, %) to oxygen tension (P<sub>O<sub>2</sub></sub>, mm Hg). If pulse oximetry indicates an oxygen saturation (S<sub>pO<sub>2</sub></sub>) of 95%, the true HbO<sub>2</sub> may be as low as 90% or as high as 100%, because the accuracy of pulse oximetry is  $\pm 5\%$ . As indicated, the S<sub>pO<sub>2</sub></sub> will change if the oxyhemoglobin dissociation curve shifts (eg, because of a change in pH), even though there is no change in arterial partial pressure of oxygen (P<sub>aO<sub>2</sub></sub>).

published, each comparing the pulse oximetry saturation (S<sub>pO<sub>2</sub></sub>) to the saturation of a simultaneously-obtained arterial sample measured on a CO-oximeter. At saturations  $> 80\%$ , the accuracy of pulse oximetry is about  $\pm 4-5\%$ .<sup>87</sup> Below  $80\%$ , the accuracy is worse, but the clinical importance of this is questionable. To appreciate the implications of the limits of accuracy of pulse oximetry, one must consider the oxyhemoglobin dissociation curve (Fig. 3). If the pulse oximeter displays an S<sub>pO<sub>2</sub></sub> of 95%, the true saturation could be as low as 90% or as high as 100%. If the true saturation is 90%, the P<sub>O<sub>2</sub></sub> will be about 60 mm Hg. If the true saturation is 100%, however, one does not know how high the P<sub>O<sub>2</sub></sub> might be. Also, a shift of the oxyhemoglobin dissociation curve can change the S<sub>pO<sub>2</sub></sub> although no change in P<sub>aO<sub>2</sub></sub> has occurred. Carlin et al<sup>96</sup> reported that the use of pulse oximetry could result in incorrect qualification of patients for long-term oxygen therapy, compared to measurement of P<sub>aO<sub>2</sub></sub> (Fig. 4). For quality control purposes, S<sub>pO<sub>2</sub></sub> should be validated periodically, which can be done with an inexpensive commercial device that simulates the human finger to produce S<sub>pO<sub>2</sub></sub> measurements.<sup>97</sup>

### Misunderstandings By Those Who Use Pulse Oximetry

Although pulse oximetry is commonly used, it may be misunderstood by those using it. Stoneham et al<sup>98</sup> reported that a large percentage of junior physicians and staff nurses lacked knowledge and made serious errors in the interpretation of S<sub>pO<sub>2</sub></sub>.

### Differences between Devices and Probes

The pulse oximeter is unique in that it requires no user calibration. However, manufacturer-derived calibration

Table 4. Minimal Requirements for Blood Gas Systems Monitors

|                                                                                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Must accurately measure P <sub>O<sub>2</sub></sub> , P <sub>CO<sub>2</sub></sub> , pH, and temperature, with a rapid response time                                                          |
| Must not have any interference from substances normally found in arterial blood                                                                                                             |
| Must operate with a 20-gauge arterial catheter without affecting continuous blood pressure measurement, collection of blood samples, or any other functions of the arterial catheter system |
| Must be biocompatible and nonthrombogenic                                                                                                                                                   |
| Must be simple to operate and maintain                                                                                                                                                      |
| Must be able to withstand the rigors and abuse of everyday practice in the intensive care unit                                                                                              |
| Must be accurate and precise for at least 72 hours                                                                                                                                          |
| Must not be adversely affected by reductions in local blood flow or perfusion                                                                                                               |
| Must not be adversely affected by changes in hemodynamics                                                                                                                                   |
| Must be cost-effective                                                                                                                                                                      |

P<sub>O<sub>2</sub></sub> = partial pressure of oxygen.

P<sub>CO<sub>2</sub></sub> = partial pressure of carbon dioxide.

Adapted from Reference 53.

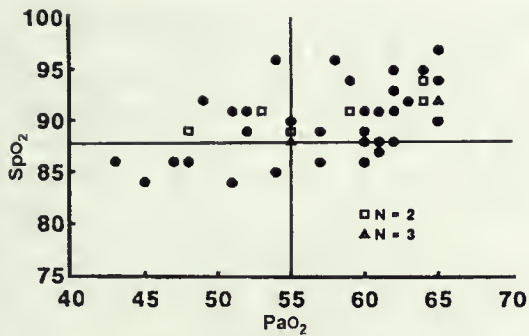


Fig. 4. The use of pulse oximetry can result in incorrect qualification of patients for long-term oxygen therapy. Note that the patients who fall in the upper left quadrant of the graph (oxygen saturation measured via pulse oximetry [ $S_{pO_2}$ ] > 88% and arterial partial pressure of oxygen [ $P_{aO_2}$ ] < 55%) would qualify for long-term oxygen based on their  $P_{aO_2}$  measurement (arterial partial pressure of oxygen measured via blood gas analysis) but would not qualify based on their  $S_{pO_2}$  measurement. Conversely, the patients who fall in the lower right quadrant of the graph ( $S_{pO_2}$  < 88% and  $P_{aO_2}$  > 55%) would qualify for long-term oxygen based on their  $S_{pO_2}$  measurement but would not qualify based on their  $P_{aO_2}$  measurement. (From Reference 96, with permission.)

curves programmed into the software vary from manufacturer to manufacturer, and can vary among pulse oximeters of a given manufacturer. Moreover, the output of LEDs can vary from probe to probe. Thus, the accuracy of pulse oximetry varies among devices,<sup>99-105</sup> so the same pulse oximeter and probe should be used for each  $S_{pO_2}$  determination on a given patient.

### Penumbra Effect

If the finger pulse oximetry probe does not fit correctly, light can be shunted from the LEDs directly to the photodetector.<sup>105</sup> Theoretically, this would cause a falsely low  $S_{pO_2}$  if  $S_{aO_2}$  is > 85% and a falsely high  $S_{pO_2}$  if  $S_{aO_2}$  is < 85%.

### Dyshemoglobinemias

Because commercially available pulse oximeters use only two wavelengths of light, they are only able to evaluate oxyhemoglobin ( $O_2Hb$ ) and deoxyhemoglobin ( $HHb$ ). Pulse oximeters assume that carboxyhemoglobin ( $COHb$ ) and methemoglobin ( $metHb$ ) concentrations are low. Abnormal elevations of  $COHb$ <sup>106-109</sup> and  $metHb$ <sup>110</sup> both result in significant inaccuracy in pulse oximetry, and pulse oximetry should not be used when  $COHb$  and  $metHb$  are elevated. Although fetal hemoglobin may affect the accuracy of carbon monoxide oximetry, it does not seem to affect the accuracy of pulse oximetry.<sup>111</sup> Pulse oximetry has also been shown to be reliable with sickle cell anemia.<sup>112</sup>

### Endogenous and Exogenous Dyes and Pigments

Vascular dyes can affect the accuracy of pulse oximetry, with methylene blue having the greatest effect.<sup>113,114</sup> Nail polish can also affect the accuracy of pulse oximetry, and it should be removed before pulse oximetry is begun.<sup>115</sup> Hyperbilirubinemia does not appear to affect the accuracy of pulse oximetry.<sup>116,117</sup>

### Skin Pigmentation

Several studies have found that the accuracy and performance of pulse oximeters is affected by deeply pigmented skin.<sup>118-120</sup>

### Perfusion

Pulse oximeters require a pulsating vascular bed to function correctly. Under conditions of low flow (eg, cardiac arrest or severe peripheral vasoconstriction), pulse oximetry becomes unreliable. Under these conditions, an ear probe may be more reliable than a finger probe.

### Anemia

Although pulse oximeters are generally reliable over a wide range of hemoglobin levels, they become less accurate and reliable with conditions of severe anemia ( $Hb$  < 8 g/dL at low saturations, and hematocrit < 10% at all saturations).<sup>121,122</sup>

### Motion

Motion of the probe can produce considerable artifact and unreliable and inaccurate pulse oximetry readings. This problem can sometimes be corrected by using an alternate probe site (such as the ear or toe rather than the finger). A technique that uses mathematical manipulation of the pulse oximetry signals to measure and subtract the noise components of motion and low perfusion is commercially available (Masimo Corporation, Mission Viejo, California) and has been reported to be useful.<sup>123</sup>

### High-Intensity Ambient Light

Because the photodetector of the pulse oximeter is non-specific, high-intensity ambient light can produce interference. This problem can be corrected by wrapping the probe with a light barrier.

### Abnormal Pulses

Venous pulses and a large dicrotic notch have been shown to affect the accuracy of pulse oximetry.<sup>124-126</sup>

## Safety

Pulse oximetry is generally considered safe, but pressure necrosis and burns from defective probes have been reported.<sup>127-130</sup>

Studies of the impact of pulse oximetry on the number of ABGs in the emergency department have reported conflicting results.<sup>131-134</sup> Bowton et al<sup>135</sup> evaluated the use of pulse oximetry in general care units, and reported that episodes of hypoxemia were rarely documented in the medical record and had little effect on physician-directed respiratory care. A large study (> 20,000 patients) of pulse oximetry use during anesthesia and postanesthesia care found no difference in outcome.<sup>136,137</sup> Although only a weak case can be made for routine use of pulse oximetry, its use should not be withheld when it is indicated. Pulse oximetry is indicated in unstable patients likely to desaturate, in patients receiving a therapeutic intervention that is likely to produce hypoxemia (such as bronchoscopy), and in patients having interventions likely to produce changes in arterial oxygenation (such as changes in  $F_{IO_2}$  or positive end-expiratory pressure). The pulse oximeter is probably no better at detection of a disconnect than the alarms already available on the ventilator. The most frequent false-positive alarms have been reported from pulse oximetry.<sup>138-141</sup>

Jubran and Tobin evaluated the use of pulse oximetry in titrating supplemental oxygen in 54 critically ill ventilator-dependent patients (Fig. 5).<sup>119</sup> In white patients, they found that an  $S_{pO_2}$  of 92% was reliable in predicting a  $P_{aO_2} \geq 60$  mm Hg. In black patients, however, an  $S_{pO_2}$  of 95% was required. Although this method is useful to titrate a level of arterial oxygenation that does not produce hypoxemia, it does not eliminate the need for periodic ABG. When pulse oximetry is used to titrate  $F_{IO_2}$ , the final  $F_{IO_2}$  setting should be confirmed by ABG analysis.

If pulse oximetry is to be clinically useful, it must have a low failure rate. Intraoperative pulse oximetry failure was evaluated by Freund et al.<sup>142</sup> Overall, they found a failure rate of < 5%. Pulse oximetry failures tended to be greater in older patients, sicker patients, and during longer surgical procedures. Failure of pulse oximetry in other settings has not been reported. Perhaps the most frequent cause of pulse oximetry failure in the ICU is accidental disconnection or misplacement of the probe.

## Transcutaneous Partial Pressure of Oxygen

Transcutaneous measurement of partial pressure of oxygen ( $P_{tcO_2}$ ) became clinically available in the mid-1970s. This technology has been most commonly used in the neonatal ICU. A number of issues have limited the use of  $P_{tcO_2}$  (Table 5), and  $P_{tcO_2}$  monitoring has declined since the introduction of pulse oximetry. Many commercially available transcutaneous monitors use a combination  $P_{tcO_2}/P_{tcCO_2}$  electrode.

The  $P_{tcO_2}$  electrode uses a polarographic principle similar to that used in blood gas analyzers.<sup>143-147</sup> To achieve a  $P_{tcO_2}$  approximating  $P_{aO_2}$ , the electrode must be heated to approximately 44° C. The close relationship between  $P_{aO_2}$  and  $P_{tcO_2}$  in neonates is the result of a complex set of physiologic events. Simply stated, the increase in  $P_{O_2}$  caused by heating roughly balances the decrease in  $P_{O_2}$  caused by skin oxygen consumption and the diffusion of oxygen across the skin. The close relationship between  $P_{aO_2}$  and  $P_{tcO_2}$  that occurs in neonates is probably more coincidental than physiologic. Failure to recognize this creates the illusion that  $P_{tcO_2}$  is the same as  $P_{aO_2}$ . In adults, the  $P_{tcO_2}$  is frequently less than  $P_{aO_2}$ . The relationship between  $P_{tcO_2}$  and  $P_{aO_2}$  in adults is too variable to allow  $P_{tcO_2}$  to be a useful reflection of  $P_{aO_2}$ . This has been shown in several recent reports, including a large multi-institution study.<sup>148-150</sup>

The relationship between  $P_{tcO_2}$  and  $P_{aO_2}$  is given by the  $P_{tcO_2}$  index ( $P_{tcO_2}/P_{aO_2}$ ).<sup>147</sup> This index decreases with age because of progressive changes in skin thickness and perfusion. Perfusion affects  $P_{tcO_2}$ , and  $P_{tcO_2}$  may reflect oxygen delivery (the product of cardiac output and arterial oxygen content) to the skin under the electrode. In other words,  $P_{tcO_2}$  tracks  $P_{aO_2}$  when perfusion is adequate, and  $P_{tcO_2}$  tracks cardiac output when  $P_{aO_2}$  is adequate. In fact,  $P_{tcO_2}$  has been used in adults to monitor the results of vascular surgery, the intent being to evaluate perfusion rather than  $P_{O_2}$  per se.<sup>151</sup> A  $P_{tcO_2}$  index of < 0.7 reflects inadequate tissue oxygenation.

$P_{tcO_2}$  decreases with decreased cardiac output and peripheral perfusion.<sup>152-155</sup> The use of  $P_{tcO_2}$  monitoring during cardiac arrest and resuscitation has been reported.<sup>156,157</sup> Although reports in the early 1980s promoted the use of  $P_{tcO_2}$  as an indicator of the effectiveness of cardiopulmonary resuscitation, this has not become common practice, for two reasons. First,  $P_{tcO_2}$  monitoring is technically difficult, particularly during cardiopulmonary resuscitation. Second, an equilibration period of 10-15 minutes is required after placement of the  $P_{tcO_2}$  electrode, which limits its use early in the resuscitation unless the electrode was in place prior to the cardiac arrest (which is unlikely).

## Mixed Venous Blood Gases

Blood obtained from the central circulation is used to assess mixed venous oxygenation. Although either the partial pressure of oxygen in mixed venous blood ( $P\bar{v}O_2$ ) or the saturation of oxygen in mixed venous blood ( $S\bar{v}O_2$ ) can be used, mixed venous oxygenation has traditionally been assessed for  $S\bar{v}O_2$ . The mixed venous oxygenation has been commonly thought to represent tissue oxygenation.<sup>158,159</sup>  $P\bar{v}O_2$  < 28 mm Hg is associated with a high likelihood of hyperlactatemia and death.<sup>160</sup>

Intermittent sampling of mixed venous blood is associated with the same preanalytical errors as ABG analysis.

An additional error is related to withdrawal of blood from pulmonary artery catheters. If the catheter is positioned in a distal branch of the pulmonary artery, rapid aspiration can contaminate the mixed venous blood with pulmonary capillary blood.<sup>161</sup> Although the importance of this has been questioned,<sup>162</sup> it seems prudent to use a slow aspiration rate ( $< 1 \text{ mL}/30 \text{ s}$ ) when blood is sampled from a pulmonary artery catheter.

Several points are important regarding the ability of mixed venous oxygenation to reflect tissue oxygenation.  $\text{S}\bar{\text{v}}\text{O}_2$  depends on the oxygen content derived from many vascular beds and thus does not necessarily well reflect the  $\text{S}\bar{\text{v}}\text{O}_2$  of any individual vascular bed.<sup>158,159</sup> With septic shock, peripheral arteriovenous shunts open, resulting in higher-than-expected  $\text{S}\bar{\text{v}}\text{O}_2$ .<sup>163</sup>  $\text{S}\bar{\text{v}}\text{O}_2$  will also be falsely elevated (ie, *not* reflect tissue oxygenation) in patients with ventricular septal defect or cyanide poisoning.

$\text{S}\bar{\text{v}}\text{O}_2$  can be mathematically derived from the Fick Equation:<sup>159,164</sup>  $\text{S}\bar{\text{v}}\text{O}_2 = 1 - \dot{\text{V}}\text{O}_2/\text{DO}_2$ , in which  $\dot{\text{V}}\text{O}_2$  is oxygen consumption and  $\text{DO}_2$  is oxygen delivery. The relationship  $\dot{\text{V}}\text{O}_2/\text{DO}_2$  is the oxygen utilization coefficient or the oxygen extraction ratio. Thus,  $\text{S}\bar{\text{v}}\text{O}_2$  is determined by the balance between  $\dot{\text{V}}\text{O}_2$  and  $\text{DO}_2$ .<sup>164</sup>

True mixed venous blood is obtained from the pulmonary artery. Normally, oxygen saturation is slightly higher in the inferior vena cava than in the superior vena cava because of the relatively low levels of oxygen extraction relative to perfusion in the renal and mesenteric vasculature.<sup>165</sup> During periods of stress (eg, shock, hypovolemia, exercise), however, there is a drop in the oxygen saturation of the inferior vena cava so that the saturation in the superior vena cava is greater than that of the inferior vena cava. This occurs as the result of decreased renal and splanchnic perfusion during these conditions. Thus, use of central venous blood other than that obtained from the pulmonary artery may be an inadequate reflection of true mixed venous blood. Although, ideally, mixed venous blood samples should be obtained from the pulmonary artery, a high correlation between pulmonary shunt calculations using pulmonary artery samples and central venous samples (eg, right atria or superior vena cava) has been reported.<sup>165</sup>

### Venous Oximetry

The ability to continuously measure mixed venous oxygen saturation via oximetry became commercially available in the early 1980s.<sup>166</sup> This system uses a microprocessor, an optical module with light sources and photodetectors, and a flow-directed pulmonary artery catheter.<sup>166–169</sup> Using fiberoptics, light with wavelengths between 650 nm and 1000 nm is pulsed into the pulmonary artery. This light is reflected off red blood cells in the pulmonary artery and returned to the optical module via

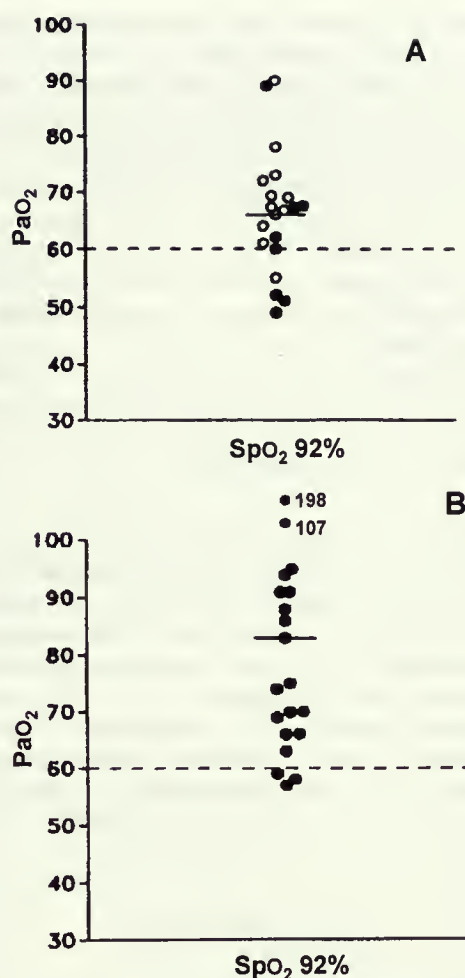


Fig. 5. A: In white patients an  $\text{S}_{\text{pO}_2}$  (oxygen saturation measured via pulse oximetry)  $\geq 92\%$  was reliable in predicting a  $\text{P}_{\text{aO}_2}$  (arterial partial pressure of oxygen)  $\geq 60 \text{ mm Hg}$ . B: In black patients, an  $\text{S}_{\text{pO}_2} \geq 95\%$  was required to reliably predict a  $\text{P}_{\text{aO}_2} \geq 60 \text{ mm Hg}$ . (From Reference 119, with permission.)

Table 5. Limitations of  $\text{P}_{\text{tcO}_2}$  Monitoring

|                                                                                         |
|-----------------------------------------------------------------------------------------|
| Frequent calibration required                                                           |
| Frequent position changes of electrode required                                         |
| Relatively long equilibration time following electrode placement                        |
| Insufficient electrode temperature may adversely affect performance                     |
| Performance may be suboptimal over poorly-perfused areas                                |
| $\text{P}_{\text{tcO}_2}$ tends to underestimate $\text{P}_{\text{aO}_2}$               |
| Compromised hemodynamic status causes an underestimate of $\text{P}_{\text{aO}_2}$      |
| Heated electrode may cause skin to blister                                              |
| $\text{P}_{\text{tcO}_2}$ may underestimate $\text{P}_{\text{aO}_2}$ during hyperoxemia |
| Frequent membrane/electrolyte changes and electrode maintenance required                |
| Performance more reliable in neonates than adults                                       |

$\text{P}_{\text{tcO}_2}$  = partial pressure of oxygen measured transcutaneously.  
 $\text{P}_{\text{aO}_2}$  = arterial oxygen tension.

another fiberoptic bundle.  $\text{S}\bar{\text{v}}\text{O}_2$  is determined by the ratio of transmitted and reflected light. Before insertion, the system is calibrated with an *in vitro* calibration standard, and this can be updated periodically by *in vivo* calibration using a carbon monoxide oximetry-determined  $\text{S}\bar{\text{v}}\text{O}_2$ . Factors that affect the measurement of  $\text{S}\bar{\text{v}}\text{O}_2$  using this method include temperature, pH, blood flow velocity, hematocrit, and occlusion of the catheter tip (eg, clot or vessel wall).<sup>166–180</sup> Although lipid emulsion infusions affect CO-oximetry, *in vivo* venous oximetry appears to be unaffected by lipid emulsion infusion.<sup>170</sup>

Several systems have been commercially available to measure  $\text{S}\bar{\text{v}}\text{O}_2$  by oximetry. Each of these uses different methods to deal with interference and drift.<sup>171,172</sup> Some use 2 reference wavelengths and one detecting fiberoptic filament, some use 3 reference wavelengths and one detecting filament (the third wavelength improves the accuracy of the system in the face of physiologic changes such as hematocrit), and some use 2 reference wavelengths and 2 detecting filaments. Some systems allow the user to periodically update the hematocrit to control the effects of hematocrit of  $\text{S}\bar{\text{v}}\text{O}_2$  measurements.

A number of studies have evaluated the accuracy of  $\text{S}\bar{\text{v}}\text{O}_2$  catheter systems.<sup>172–185</sup> Most of these reported that the 3-wavelength systems correlate better with CO-oximeter  $\text{S}\bar{\text{v}}\text{O}_2$  than 2-wavelength systems and that drift is less with 3-wavelength systems. Studies reporting bias and precision analysis have found greater degrees of inaccuracy than those claimed by the manufacturer.<sup>183–185</sup> However, if meticulous attention is paid to care of the catheter system (eg, *in vivo* calibrations, updating the hematocrit setting), either of these systems may be acceptable to detect changes or trends. These systems do require more technical attention than other monitoring systems, such as pulse oximetry or conventional pulmonary artery catheter.

Regardless of the equipment's technical performance, the clinical usefulness of  $\text{S}\bar{\text{v}}\text{O}_2$  monitoring remains unclear.<sup>162–165</sup> For example, the results of a large multicenter study (> 10,000 patients in > 50 ICUs) showed that targeting  $\text{S}\bar{\text{v}}\text{O}_2 > 70\%$  did not affect mortality.<sup>186</sup>

### Gastric Tonometry

Gastric tonometry has been suggested as a minimally invasive method to assess tissue oxygenation in critically ill patients.<sup>187–197</sup> Perfusion of the gut is affected early in the course of systemic hypoxia. Tissue hypoxia should result in a decrease in gastric intramucosal pH ( $\text{pH}_i$ ). Normal  $\text{pH}_i$  is  $7.38 \pm 0.03$ . Hypoperfusion of the gut also increases gastric intramucosal  $\text{P}_{\text{CO}_2}$ , which is referred to as regional  $\text{P}_{\text{CO}_2}$  ( $\text{P}_{\text{rCO}_2}$ ). The  $\text{P}_{\text{rCO}_2}$  can increase with either decreased perfusion or increased  $\text{P}_{\text{aCO}_2}$ . With decreased perfusion, the gap between  $\text{P}_{\text{rCO}_2}$  and  $\text{P}_{\text{aCO}_2}$ , the  $\text{P}_{(\text{r-a})\text{CO}_2}$ , increases.

The gastric tonometer consists of a nasogastric tube with a distal carbon dioxide-permeable silastic balloon. The balloon is filled with 2.5–3 mL of physiologic saline solution. An equilibration time of 1–2 hours is allowed for  $\text{CO}_2$  in the gastric lumen to equilibrate with the saline inside the balloon. After discarding 1–1.5 mL of aspirate from the gastric tube (dead volume), the remaining 1–1.5 mL is analyzed for  $\text{P}_{\text{CO}_2}$  using a blood gas analyzer. A simultaneous arterial blood sample is analyzed to determine  $\text{HCO}_3^-$ . Gastric  $\text{pH}_i$  is then calculated from the Henderson-Hasselbalch equation, using the  $\text{P}_{\text{CO}_2}$  of the saline from the gastric balloon and the  $\text{HCO}_3^-$  of the arterial blood.

Several studies have reported substantial preanalytical errors related to air contamination of the saline sample.<sup>198–200</sup> This has led to the development of gas tonometry techniques<sup>201,202</sup> and techniques using a fiberoptic probe.<sup>203</sup> Another advantage of these techniques is that they can be used for continuous or nearly continuous monitoring. The use of gastric tonometry to evaluate tissue oxygenation is controversial.<sup>204,205</sup> Its use is limited because of technical issues and uncertainty regarding its clinical value.

### Monitoring in Perspective

How much monitoring is needed? This is an important question for both clinicians and administrators. Clinicians often want to monitor everything possible, with a “more is better” attitude. On the other hand, administrators and managed care providers are justifiably concerned with the costs associated with monitoring.

The presence of many monitors at the bedside can be very distracting to clinicians. Many monitoring systems tend to beep, buzz, and blink constantly. Bentt et al found that a pulse oximetry alarm was present up to 47% of the time (28 min/h) in a 10-bed surgical ICU, and that many of these were false alarms and required no intervention.<sup>140</sup> Kestin et al<sup>141</sup> found that, during anesthesia monitoring, 75% of all alarms were spurious and only 3% indicated risk to the patient. In an adult ICU, monitor alarms were present 20% of the time, with an average peak sound level of nearly 80 dBA (the Environmental Protection Agency recommends that noise levels in hospitals not exceed 45 dBA).<sup>206</sup>

The financial impact of monitoring is difficult to assess. For noninvasive monitors such as pulse oximeters, no prospective randomized controlled trials have evaluated cost effectiveness. Using a historical control and a relatively short evaluation period (2 months), Kellerman et al<sup>132</sup> reported a reduction in the number of ABGs ordered in an emergency department following the introduction of pulse oximetry. However, others have found an increased number of ABGs when pulse oximetry was used.<sup>6</sup> For mixed

venous oximetry, Orlando reported a savings of \$75 per patient.<sup>207</sup> Pearson et al,<sup>208</sup> however, found that monitoring mixed venous saturation added significantly to the cost incurred with a routine pulmonary artery catheter. Jastremski et al<sup>209</sup> found that mixed venous oximetry may not be cost-effective, particularly in a fixed-payment reimbursement system.

Monitoring of oxygenation is often useful in patient care. However, monitoring should not be done just because it is technically feasible. Technical capability must be balanced against clinical usefulness and cost effectiveness. The decision to monitor, like any other clinical decision, should be based on therapeutic objectives.

### Recommendations for Oxygen Monitoring in Various Clinical Settings

#### Critical Care

All techniques, invasive and noninvasive, can be used to evaluate oxygenation in critically ill patients. In this setting, the issue is selection of the appropriate monitoring technique rather than using every available method.

#### Acute Care

Continuous invasive monitoring is not used outside the ICU. Continuous pulse oximetry monitoring is used, but the value of this has been questioned if a clinician is not readily available to respond to the information. More commonly, spot checks of  $S_{pO_2}$  are used. Ideally, the same pulse oximeter and probe should be used for each spot check. ABGs are commonly performed in this environment and POC testing can be used.

#### Prehospital Care

Pulse oximetry is increasingly used in the prehospital setting. POC testing could be used, but the safety of arterial puncture in the field has not been established.

#### Emergency Care

Pulse oximetry (continuous or spot checks) can be used in the emergency department. ABGs are commonly obtained in this environment and POC testing can be used. Continuous invasive monitoring of oxygenation in this environment is seldom indicated.

#### Extended Care

Pulse oximetry spot checks can be used in this environment. Of concern, however, is the correct interpretation of this information in this setting. ABGs can be obtained in

this setting, provided that a person skilled to perform an arterial puncture is available. However, ABGs have the potential for considerable preanalytical error in this setting (eg, transport delay before analysis). POC testing could be used in this setting, provided that individuals skilled in the use of this equipment are available.

#### Home Care

Monitoring oxygenation in the home is associated with the same issues as monitoring oxygenation in an extended care facility.

### Summary

Many techniques are available to evaluate oxygenation. These include arterial blood gases, capillary blood gases, point-of-care testing, blood gas monitors, pulse oximetry, transcutaneous blood gases, mixed venous blood gases, venous oximetry, and gastric tonometry. Clinicians should understand not only the benefits, but also the limitations of these techniques. Monitoring of oxygenation should not be done just because it is technically feasible. The decision to monitor, like any other clinical decision, should be based on therapeutic objectives.

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## Discussion

**MaeIntyre:** You imply, as I think most clinicians do, that the arterial blood gas is sort of the gold standard of the status of arterial oxygenation. I would just like to make a comment about the reproducibility of a blood gas. I think that's important because a lot of people make decisions on changes in blood gases that may just in fact be variability in the system. It's an important point, because there is variability and the CLIA [Clinical Laboratory Improvement Act] standards showed that to be a

certified blood gas lab you have to be within a certain variability, but that variability can be up to 10% for P<sub>O<sub>2</sub></sub>. I don't know if that's going to match your graph here or not.

**Hess:** You're exactly right.

**MaeIntyre:** Two standard deviations is close to 10%, which means that if you have someone with a P<sub>O<sub>2</sub></sub> of 60 mm Hg, and you just repeat it again, you have a very high likelihood of it actually falling or rising as much as 6 mm Hg. A lot of people make decisions on changes of only 5 mm Hg or

less. I think it's important to point out that some of that may just be biologic variability and machine variability.

**Hess:** That's an excellent point. This is a slide that I took out in the interest of time, where I was going to talk a little bit about that. This is work that I was involved with published in the early 1990s looking at spontaneous variability in P<sub>O<sub>2</sub></sub>.<sup>1</sup> Dr Pierson's group published some similar work I believe in the early 1980s in *Chest*,<sup>2</sup> and since that there have been two or three additional studies indicating that, particularly in critically ill patients, there is

a lot of spontaneous variability in  $P_{O_2}$ , making the point that if the patient has a  $P_{O_2}$  of 70 mm Hg and then you get a repeat blood gas, and it's 60 or 80 mm Hg, then perhaps we ought not to overreact to that too much. So your point is well taken.

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**Wedzicha:** Dean, thank you very much. I'd like to just say something about ear lobe blood gases.

**Hess:** Yes, since I've referred to some of your work.

**Wedzicha:** One of the reasons that we are so keen on ear lobe blood gases is that, in the UK, nurses and respiratory therapists cannot do arterial blood gases; only doctors are allowed to do those. Consequently, for practical reasons we have problems if we have large clinics involving patients with chronic hypoxemia like I do, or, indeed, ventilator patients. We absolutely need ear lobe blood gases to get measurements of  $CO_2$ , especially with the ventilator patients. So we do a lot of them, and over the years we've looked quite regularly at the performance of ear lobe versus radial artery, and in our unit we have very good agreement. There is one very important technical point, and that is that when ear lobe gases are done you do need the blood from the ear lobe to be free flowing to get good results.

**Hess:** Probably because there's less room air contamination.

**Wedzicha:** Absolutely. That is right. What actually happens is that we train

our technicians not to take ear lobe gases unless there is free flow. I think this is where the problem has emerged that perhaps technicians often do them who are not so experienced in actually getting the blood out of the ear. I would still maintain this is a very useful technique, especially where practically you cannot do radial blood gases.

**Hess:** What about the use of the technique to look at pH and  $P_{CO_2}$ ? Could one make an argument that using the pulse oximeter (appreciating the issues that I went over) to look at oxygenation, and then use the arterialized capillary sample to look at  $P_{CO_2}$  and pH?

**Wedzicha:** Mostly for  $P_{CO_2}$ . Again, the agreement is excellent. We avoid arterialized gases when people have acute exacerbations and acute or chronic respiratory failure. That's when you get reduction in cardiac output, etc, and you tend to get worse samples.

**MacIntyre:** Let me just ask about the role of this so-called spot check (pulse oximetry testing). There's a tendency, certainly in my hospital and other places I've visited, where the respiratory therapists (sometimes it's the nurse) actually starts treating the pulse oximetry measurement as almost the "fifth vital sign." They just do it routinely. They do it twice a day. Pulse-ox testing. I've often wondered what the utility of that is in a patient who doesn't have any other signs or symptoms of hypoxemia. I've sort of glibly put up an announcement in my hospital that if anyone could find an instance where a routine pulse-ox, without any other signs or symptoms, detected an important change in patient status, I was going to give them a steak dinner. I still haven't paid that bet yet. That was an offer I made some 5 years ago, and I'm just kind of interested from the group around the table

here if anyone has seen a case where a spot check  $S_{pO_2}$ , out of the blue, with no other reason to do it other than the fact that it was a routine, found something that was clinically important and wouldn't have been detected otherwise? And Josh raises his hand.

**Benditt:** We found 2 cases of methemoglobinemia in lung transplant patients who were taking dapson. We diagnosed it using that, with nothing else.

**Hess:** Methemoglobinemia?

**Benditt:** Yes.

**Hess:** Tell us about that.

**Benditt:** Well, I guess I shouldn't say there were no other symptoms. The patient complained of shortness of breath, and we got blood gases and oximetry. And there was a discordance between those, and we diagnosed . . .

**Hess:** OK, so the diagnosis was actually because of a discordance, as you say, between the arterial saturation and the pulse oximeter saturation. That's a little bit different than I think what Neil is saying, is that a nurse or a respiratory therapist on some routine basis records the oxygen saturation, and that's the only piece of information that you have.

**MacIntyre:** So I take it my steak dinner is still safe.

**Hess:** There is actually some evidence in the literature that has looked at this, suggesting that routine monitoring of pulse oximetry in patients outside of an intensive care unit (ICU) has a very low yield.

**MacIntyre:** I'm fascinated with some newer technology looking at tissue oxygenation. In addition to gastric pH, I remember a couple years ago there was a device that utilized a near

infrared scope or a monitor that you could stick on the forehead, and it would supposedly give you brain cytochrome status as an index of tissue hypoxia. I haven't seen much about that recently. Is anyone here aware of its status?

**Hess:** I'm not aware of that.

**MacIntyre:** It's called a niroscope (near infrared optical scope). I'm not sure where it ever went in development, but it was a clever idea. It was looking at the oxidative state of brain tissue with a noninvasive monitor.

**Hess:** There are jugular venous oximeters, as you know, that are used in neurological ICUs to look at cerebral oxygen uptake and so forth.

**McCoy:** Dean, I've got a question for you and for the group. What's your feeling on using oximetry to trend a patient in the home care setting? The reason for the question is that there's a company working on an oxygen-conserving device that would be controlled by an oximeter. The question would be, is the oximeter reliable enough to control oxygen dosing?

**Hess:** I would be very concerned about that. I think there are a lot of issues with precision and bias in pulse oximetry that could create, I believe, some real issues with that. The issue of trending often comes up with these kinds of monitoring devices, whether they are oximeters, capnographs, or other types of monitoring devices, and many times the correct studies have not been done to show whether these are good trending devices or not. The way you would need to do that study is not put the pulse oximeter on the patient and then show the pulse oximeter goes up and down over time. What you would need to have is something to compare that to. I don't think those types of comparison studies have ever been done for many of the monitors that we use where the man-

ufacturers claim that even though it's not very accurate, it's a good trending device. I don't think the correct experiments have been done to show whether they're good trending devices or not.

**Kacmarek:** I would take a little different stance than Dean, and believe that there might be a potential for oximetry in the home if you use the same oximeter, the same probe, the same location, the same circumstances under which you did the evaluation on a routine basis. The standardization of the equipment and the circumstances in which you do the analysis may end up resulting in much better accuracy than the literature currently shows, particularly considering Neil's comments on the inaccuracy of blood gases and Dean's comments on the normal day-to-day variability that we might find if studies were done carefully. The variability may not be that great if you can standardize every factor possible.

**Hess:** One of the other issues, though, that needs to be dealt with is how well the device deals with artifact, and whether it has appropriate algorithms for artifact rejection. Because you wouldn't want the device varying the inspired oxygen because the patient wiggles their finger or because they move it from one finger to another, or because their house is a little bit colder that day so they don't get as good perfusion into their finger. I think one of the criteria for the type of technology you're referring to, Bob (Kacmarek) and Bob (McCoy), would have to be how well does the device know that there is not artifact that it's dealing with rather than a true change in the oxygen saturation.

**Kacmarek:** As you well know, if you compare a pulse oximeter of today with one from 10 or 15 years ago, there have been significant improvements in identifying artifact and avoiding the display of inaccurate data. It

seems to me it's just a matter of time until that technology is refined to the point that we can depend on the data provided in the home. I agree with your concerns, but I don't think that the problem is insurmountable. I think it's a matter of coming up with the correct technologic solution to allow pulse oximetry to be utilized in the home accurately.

**Hess:** The next question would be, will that device, which is much better than what we have now, also still be affordable? Improvement in technology will probably come with an increase in cost.

**Petty:** I'm involved with a limited number of medical malpractice cases, and within the past year I've reviewed 2 cases, one in status asthmaticus and another patient with overwhelming pneumonia, where the only monitoring was oximetry. Oximetry was normal right up to the time of cardiac arrest. So I think our fascination with the oximeter has really got a down side. We're forgetting about pH and  $P_{CO_2}$  in these settings.

**Dunne:** Just a comment on the marriage of the pulse oximetry technology with oxygen-conserving devices. The problem as I see it in the home care industry is that as we start to reduce or miniaturize the size of pulse oximeters to make them an ambulatory device, we increase the risk of equipment abuse. The device is no longer treated as a delicate piece of medical equipment, but rather as a commodity. So it seems to me that there is another issue here, which is the treatment of the machinery itself once it is miniaturized and placed in the field, in the uncontrolled environment we don't normally expect to see in an ICU or a more controlled environment in the hospital.

**Hess:** I would just add that these devices aren't that well taken care of in the ICU, either.

**McCoy:** From what Dr Petty was saying about a lot of patients being overprescribed, one of the things is that if you have continuous oximetry monitoring, it's better than what we have now, which is no monitoring, so there's an awful lot of oxygen therapy that's going on in home care that may

not be indicated. One of the things that this company has that I thought was fascinating (since everyone wants to have the greatest savings-conserving device out there) is that their device actually shuts off if there is no oxygen required, which is the only way a device can really save a lot of oxy-

gen. All the other devices fire every time a patient takes a breath.

**Hess:** Maybe I would just take issue with your point that some monitoring is better than no monitoring. I would argue that inaccurate monitoring is worse than no monitoring.

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# Delivery Systems for Long-Term Oxygen Therapy

Robert M Kacmarek PhD RRT FAARC

## Introduction

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## Summary

[Respir Care 2000;45(1):84–92] *Key words: long-term oxygen therapy, gas cylinder, oxygen concentrator, liquid oxygen, flow calculation, oxygen enricher, portable oxygen.*

## Introduction

Oxygen was originally discovered by Joseph Priestley in 1774 and named by Lavoisier shortly thereafter.<sup>1</sup> For over 200 years there have been reports on the use of oxygen in the medical literature. However, it wasn't until 1888 that practical systems allowed oxygen delivery to become available on a widespread basis. Cylinders of compressed gaseous oxygen were introduced for medical as well as commercial use in 1888.<sup>1</sup> Liquid oxygen systems for hospital use became available in the early 1900s but it was not until the 1960s and 1970s that liquid oxygen for use outside the hospital became readily available. In 1974 the first oxygen concentrator was introduced for delivery of home oxygen therapy.<sup>1</sup> Today three systems (gas cyl-

inders, liquid oxygen systems, and oxygen concentrators) are available for delivery of long-term oxygen therapy (LTOT) in the home.

## Gas Cylinders

In spite of gas cylinders being large, awkward, and heavy, they remain the primary method of providing LTOT worldwide. However, in the United States, most would consider them second in frequency, behind oxygen concentrators. This discrepancy is essentially based on the relationship between the cost of labor versus the cost of technology in a given country. In the highly developed countries of North America, Western Europe, and Japan, the use of cylinders in the home is low, estimated at  $\leq 10\%$  of total home LTOT use. In less developed countries, where labor costs are lower but technology costs are higher, cylinders are the primary method of providing ( $> 90\%$ ) home oxygen therapy.

## Available Cylinder Sizes

As illustrated in Figure 1, there are numerous different cylinder sizes available for home use, ranging from the

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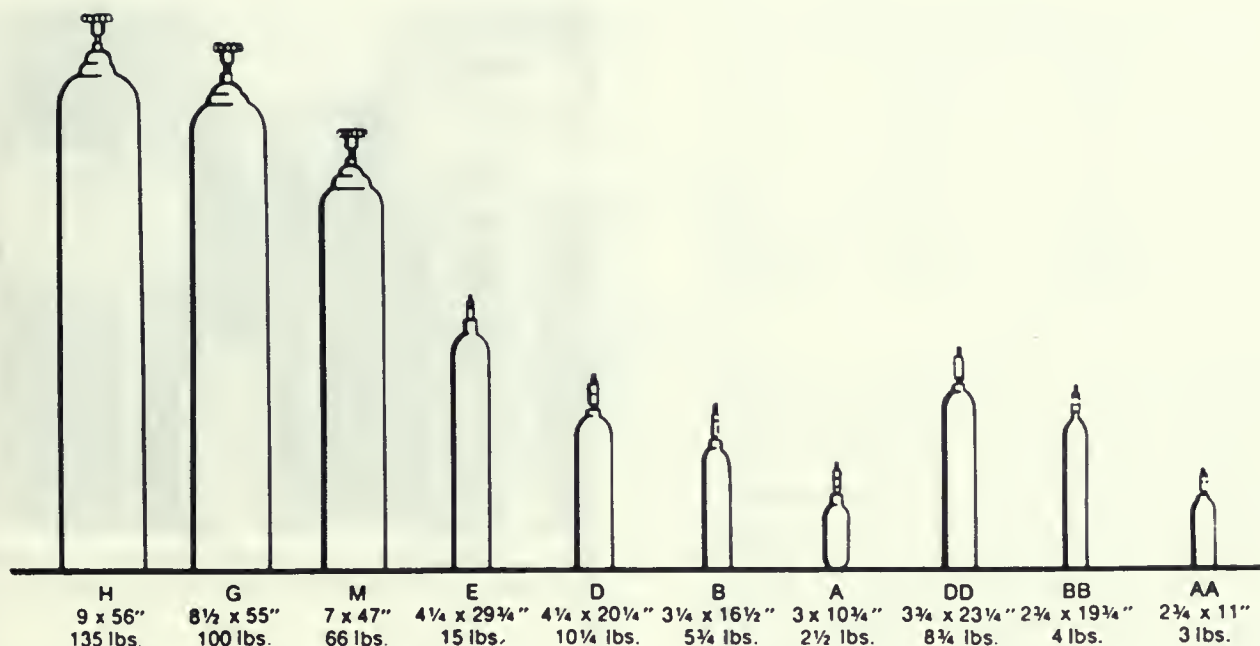


Fig. 1. Letter designation and approximate dimensions of high-pressure medical gas cylinders. (From Reference 2, with permission.)

very large H cylinders to the quite small A cylinders.<sup>2</sup> In addition to the sizes mentioned in Figure 1, many manufacturers have developed alternative sizes of small portable cylinders. Specifically for use in the home, many manufacturers have developed aluminum cylinders that are < 50% of the weight of similar size steel cylinders (Fig. 2). In spite of the size variability, the biggest problem associated with cylinders is their limited gas volume. As shown in Table 1, even the large H cylinders can provide a continuous oxygen flow of 2 L/min for only slightly longer than 2 days. As a result, patients with H cylinders in the home must have adequate space to store several cylinders, so as to limit cylinder delivery to once a week.

An additional problem with cylinders is changing the regulator from one cylinder to the next. This task is considered formidable by many hospital staff and can be daunting for patients and family. Storage and maintenance of compressed gas cylinders in the home also present the same hazards that exist in the hospital: concern regarding fire hazard, avoidance of the use of oils or grease near the cylinders, and care in handling the cylinders to avoid injury from the weight of the cylinder or as a result of fracture of the cylinder stem.

#### Duration of Flow

As a result of the limited gas volume in cylinders, it is critical that the duration of flow be accurately estimated regardless of cylinder size. Table 2 shows the two formulas needed to estimate the duration of flow from any cyl-



Fig. 2. Aluminum oxygen cylinders for home use. (Courtesy of Invacare, Elyria, Ohio.)

inder.<sup>3</sup> A duration of flow factor for specific cylinder sizes can be determined by multiplying the number of cubic feet present in a cylinder by 28.3 L/ft<sup>3</sup> (to convert cubic feet to

Table 1. Duration of Oxygen Flow from Cylinders at 2 L/min

| Size | Factor | Liters | Time         |
|------|--------|--------|--------------|
| H    | 3.14   | 6908   | 57 h, 33 min |
| G    | 2.41   | 5302   | 44 h, 11 min |
| M    | 1.65   | 3625   | 30 h, 12 min |
| E    | 0.28   | 616    | 5 h, 8 min   |
| D    | 0.16   | 352    | 2 h, 56 min  |
| B    | 0.068  | 150    | 1 h, 15 min  |
| A    | 0.035  | 76     | 38 min       |

liters) and then dividing the result by the maximum cylinder operating pressure. The duration of flow factors for all common cylinder sizes are listed in Table 1.<sup>3</sup> To determine how long a cylinder will last at a given flow, the pounds per square inch (psi) pressure in the cylinder is multiplied by the duration of flow factor and then divided by the set liter flow. As illustrated in Table 1, the duration of flow with small cylinder sizes at 2 L/min is extremely short. A D size cylinder will last only 2 hours and 56 minutes at 2 L/min.<sup>4</sup>

### Advantages of Gas Cylinders

Gas cylinders always provide 100% oxygen and are capable of delivering whatever liter flow is indicated to meet the oxygenation requirements of a given patient. Regardless of the type of oxygen therapy equipment in the home, gas cylinders are capable of providing the driving pressure necessary for operation. In addition, gas cylinders are universally available.

### Liquid Oxygen

The use of liquid oxygen has been promoted based on the ability of these systems to contain a very large reservoir of gas in a very small space (Fig. 3), because 1 ft<sup>3</sup> of liquid oxygen is equal to 860.6 ft<sup>3</sup> (24,355 L) of gaseous oxygen.<sup>3</sup> A more convenient relationship is that 1 L of liquid oxygen equals 840 L of gaseous oxygen. A typical

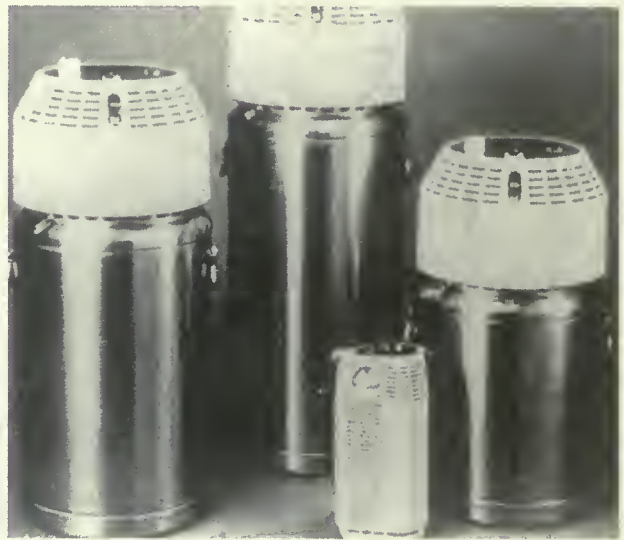


Fig. 3. Typical stationary liquid oxygen system with a portable liquid oxygen system. (Courtesy of Mallinckrodt, Pleasanton, California.)

home liquid oxygen system contains at maximum about 40 L of liquid oxygen (33,600 L of gaseous oxygen). At 2 L/min that system will provide oxygen for > 11 days. An additional advantage of liquid oxygen systems is that every manufacturer of these systems also provides portable liquid oxygen systems that can be transfilled from the in-home stationary system.<sup>1,5,6</sup> Today most in-home stationary systems are relatively compact and have wheels that allow some mobility about the house.

### Operation of Liquid Oxygen Systems

In-home liquid oxygen systems are essentially a miniaturized version of the large liquid oxygen reservoirs used by hospitals. The container is designed like a thermos bottle to prevent heat transfer, keeping the liquid at -297.3° F.<sup>7</sup> As with all thermos bottles, the insulating capability is not perfect and there is continual loss of oxygen if not in use. Loss from most systems is estimated at 0.055 lbs/h or 40–50 L of gaseous oxygen per hour.<sup>4</sup> Typically, the pressure over the liquid oxygen in these systems is 20 psi.<sup>4</sup>

Figure 4 illustrates the structure of a home liquid oxygen reservoir system. These units incorporate a flow control valve for direct delivery of oxygen and a quick-connect attachment with which to fill small portable liquid oxygen systems (Fig. 5). The direct flow of oxygen from the unit is provided from the gas sitting over the liquid via an economizer valve and warming coils that lead to the flow control valve.<sup>4–6</sup> When the gas pressure over the liquid decreases to 0.5 psi, the economizer valve closes and liquid oxygen is drawn up the liquid withdrawal tube through the vaporizing and warming coils where it is con-

Table 2. Determination of Available Flow from Gas Cylinder

|                                        |                                                                                            |
|----------------------------------------|--------------------------------------------------------------------------------------------|
| Calculation of L/psi conversion factor | Conversion factor = $\frac{(\text{cu ft full}) (28.3 \text{ L/cu ft})}{\text{psi full}}$   |
| Example: H cylinder                    | $3.14 \text{ L/psi} = \frac{(344 \text{ cu ft}) (28.3 \text{ L/cu ft})}{2200 \text{ psi}}$ |
| Duration of Flow Formula               | Minutes = $\frac{(\text{psi}) (\text{factor})}{\text{flow}}$                               |
| Example: H cylinder                    | $2355 \text{ min (39 h 15 min)} = \frac{(1500 \text{ psi}) (3.14)}{2 \text{ L/min}}$       |

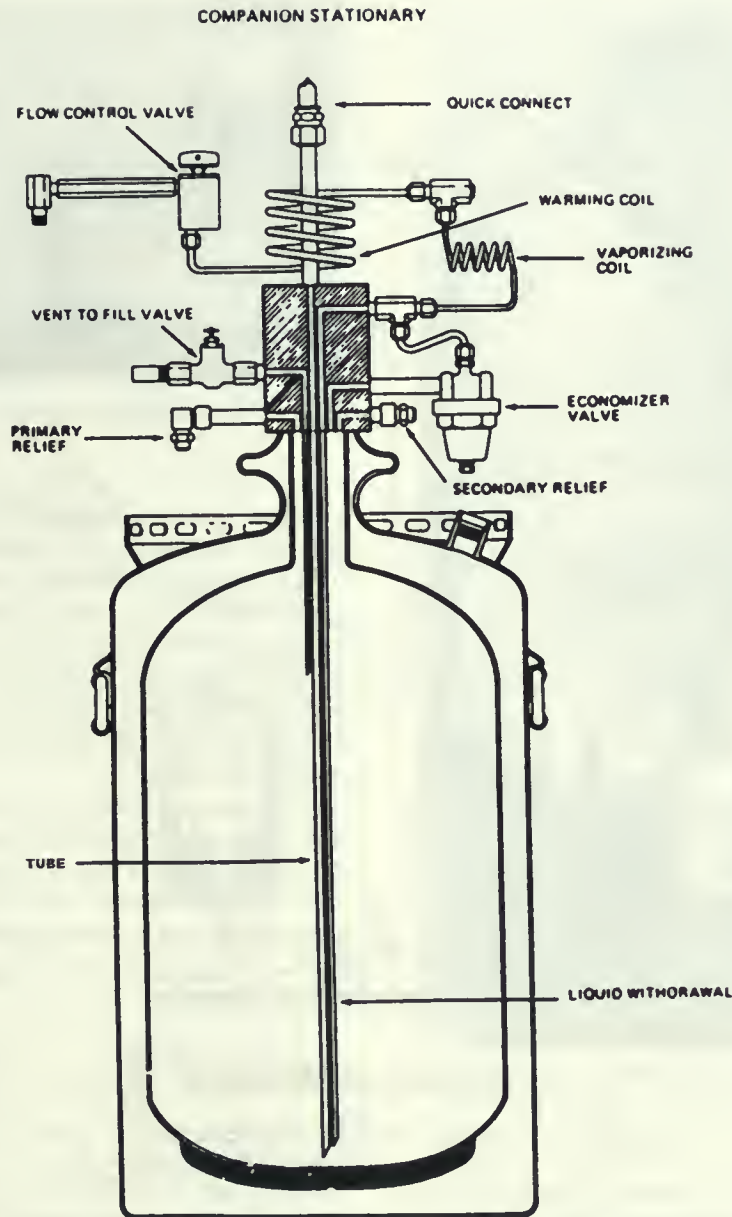


Fig. 4. Structure of a stationary liquid oxygen container. See text for discussion (Courtesy of Mallinckrodt, Pleasanton, California.)

verted to a gas. As a result, a constant flow of oxygen is maintained. When not in use, gas formed by evaporation is released from the primary pressure relief valve (2 psi over maximum working pressure) or the secondary pressure relief valve (10 psi over maximum working pressure) if the primary valve fails.<sup>4-6</sup>

#### Advantages/Disadvantages

Liquid oxygen systems have the advantage of storing a large quantity of 100% oxygen in a small place. They also

allow for moderate gas flows of  $\leq 8$  L/min and all have small companion portable systems.<sup>7</sup> However, many home care providers consider liquid oxygen systems very expensive. The capital investment is very high. Not only must the actual reservoir and portable unit be purchased, but trucks capable of transporting liquid oxygen must also be purchased. In addition, labor costs are high since most of these units must be filled every 10–14 days. Transfilling of portable liquid oxygen systems (see Fig. 5) is complex and frightening to many patients. Thermal burns are possible during transfilling,<sup>6,7</sup> and there is the potential of



Fig. 5. Transfilling of a portable liquid oxygen system. (From Reference 1, with permission.)

liquid oxygen exiting the unit during prolonged high-flow use, which can also lead to thermal burns. Spillage of liquid oxygen is possible if the unit is tipped. Also, during transfilling and high-flow use, units may freeze, preventing further operation.<sup>4-7</sup>

### Concentrators

The most commonly used home oxygen delivery system in the United States is the oxygen concentrator (Fig. 6). Currently, at least a half dozen companies manufacture oxygen concentrators. Figure 7 shows a schematic of a typical oxygen concentrator.<sup>8</sup> Room air is drawn into the unit through a series of particle filters, into a compressor, through an additional particle filter, then to a heat exchanger to dissipate the heat of compression.<sup>4,8</sup> Gas is then directed to one of a series of molecular sieve beds by a



Fig. 6. Typical oxygen concentrators. (Courtesy of Invacare, Elyria, Ohio.)

solenoid controller. Within the molecular sieve, room air is separated into oxygen and nitrogen plus trace gases.<sup>4,7,8</sup> This is accomplished by granular crystal zeolite, which is approximately 5 angstroms in diameter. Zeolite can separate gases based on size and polarity. The concentrated oxygen is stored in a small cylinder for delivery to a flow meter. When a sieve bed is filled, room air is diverted to another bed while nitrogen and other gases are exhausted to the atmosphere.<sup>4,5</sup>

Oxygen concentrators are able to deliver high oxygen concentrations but not 100% oxygen.<sup>9-11</sup> As shown in Table 3, the fraction of inspired oxygen ( $F_{IO_2}$ ) depends on the flow rate. Flow rates of  $\leq 2$  L/min are most efficient in maintaining high oxygen concentration.<sup>12</sup>

### Oxygen Enricher

An alternative approach to providing oxygen from room air is the oxygen enricher.<sup>1,4,7</sup> Although there still are a few of these devices in use, I do not believe anyone is manufacturing them today. The major difference between concentrators and enrichers is the concentration of oxygen available. With concentrators the  $F_{IO_2}$  is generally  $\geq 90\%$ , but with enrichers the  $F_{IO_2}$  is about 40%.<sup>7</sup> As a result, only the equivalent of about 2 L/min of oxygen is available. The recommendation is to set the delivered flow 3 times the desired setting with 100% oxygen.<sup>1</sup> That is, if 2 L/min of oxygen is prescribed, a flow of 6 L/min is set on the enricher.

The difference in  $F_{IO_2}$  is based on the mechanism of action. Enrichers separate oxygen and water vapor from other environmental gases by diffusion across a 1-mm-thick plastic membrane.<sup>3,4,7</sup> One advantage of the enricher is that it also concentrates water vapor to 3 times the ambient level.<sup>4</sup> In actual operation, water vapor has to be removed from the filtered gas prior to delivery to the patient. It was the inability of enrichers to provide an  $F_{IO_2} > 0.40$  that drove them from the market.

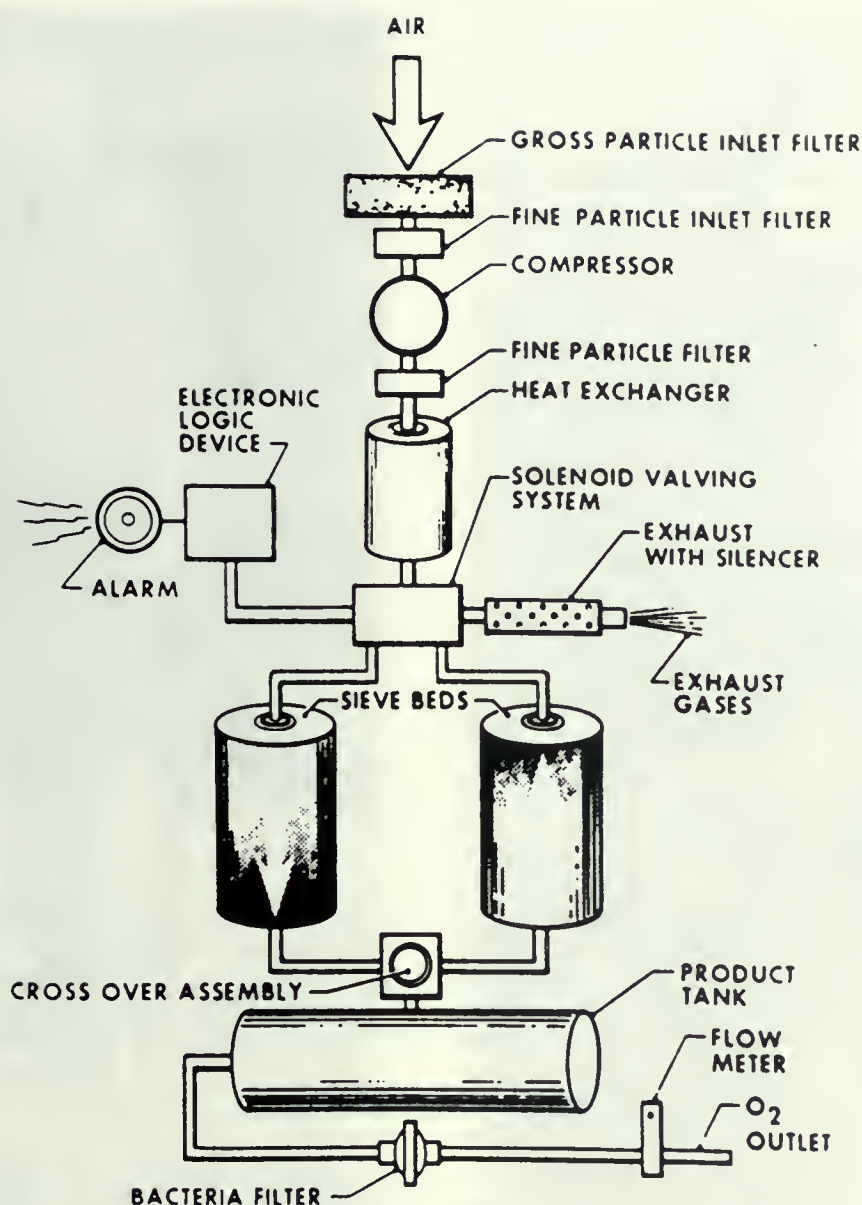


Fig. 7. Molecular sieve oxygen concentrator. See text for discussion. (From Reference 8, with permission.)

### Portable Systems

Although all home oxygen delivery systems can be classified as moveable, a truly portable system requires very

specific features. These systems must be both lightweight and compact, and capable of providing oxygen for extended periods. At least theoretically, all three delivery

Table 3. Output of Oxygen Concentrators

| Liter Flow     | Concentration        |
|----------------|----------------------|
| $\leq 2$ L/min | $F_{IO_2} \geq 0.95$ |
| 3–5 L/min      | $F_{IO_2} \geq 0.90$ |
| $> 5$ L/min    | $F_{IO_2} < 0.90$    |

Table 4. Portable Oxygen Therapy Delivery Systems

| System                         | Weight        | Maximum Duration of Flow at 2 L/min |
|--------------------------------|---------------|-------------------------------------|
| Gas tank (aluminum E cylinder) | 7.5 lbs       | 5 h, 8 min                          |
| Liquid oxygen (1 L system)     | 4–7 lbs       | 7 h                                 |
| Concentrator                   | $\leq 30$ lbs | Depends on battery size             |

systems (cylinders, liquid oxygen, and concentrators) can be portable. Table 4 compares the three approaches.

### Oxygen Cylinders

Again, worldwide as well as in the United States, small oxygen cylinders are the most common method of providing portable oxygen. From a practical perspective, portable oxygen cylinders should be of E size to ensure that oxygen therapy is available for an extended period. With an E-size cylinder, a maximum of 5 hours of oxygen at 2 L/min is available. As shown in Figure 8, a major problem with portable gas cylinders is size and ease of movement. Although portable gas cylinders can be made lighter, they cannot be made smaller. As discussed in other papers of this conference, some patients requiring oxygen therapy have poor self-images and are concerned about the reaction of the public to their need for oxygen. As stated by Thomas Petty at this conference, patients having to "schlep" an E cylinder around tend to draw attention to themselves. As shown in Figure 1 and Table 1, smaller cylinders, which can be carried in a backpack, are available but, of course, their flow duration is very limited.

### Liquid Oxygen System

Liquid oxygen systems would seem the ideal portable oxygen delivery system. They are small, compact, can carry a large volume of oxygen in a small space, and many incorporate oxygen-conserving devices (Fig. 9). As shown in Table 4, the typical portable liquid oxygen system holds 1 L of liquid oxygen (840 L of gaseous oxygen), weighs 4–7 lbs, and is capable of providing oxygen at 2 L/min for a maximum of 7 hours.<sup>1,3</sup> Much longer times are available if an oxygen-conserving device is included.<sup>6</sup> Other portable liquid oxygen systems hold 1.5 L of liquid oxygen, increasing the system weight by about 40% but also increasing the duration of available 2 L/min oxygen flow to over 10 hours.

The primary drawback to liquid oxygen systems is cost of operation. The capital cost, ongoing labor costs, and continually decreasing reimbursement for home oxygen therapy have reduced the percentage of patients using liquid oxygen systems in the United States to < 10% and have prevented liquid oxygen systems from being introduced into many parts of the world.

### Concentrators

Although at first discussion it would not seem feasible to use a concentrator for portable oxygen, portable systems are nevertheless available (Fig. 10).<sup>1</sup> Size and weight are of primary concern with these systems. However, airlines now have access to concentrators that can be placed under



Fig. 8. Portable oxygen E cylinder. (From Reference 1, with permission.)

the patient's airplane seat. Even smaller concentrators will probably become available, making them yet more portable, and when this occurs, the primary limitation of these systems will be battery life. Once a lightweight, long-duration, rapidly-rechargeable, inexpensive battery is available, I would expect concentrators will become the standard for portable oxygen therapy.

### Innovation

As with all aspects of medicine, ongoing research to improve home oxygen delivery systems is active. The most



Fig. 9. Portable liquid oxygen system. (Courtesy of Mallinckrodt, Pleasanton, California.)

recent innovation is depicted in Figure 11.<sup>13</sup> Two companies make oxygen concentrators that are also able to fill portable oxygen cylinders. This ability greatly reduces the cost and inconvenience of portable systems. It can be expected that additional such systems, operating more efficiently, will be available in the future.

In addition, there is at least one group working on an oxygen concentrator system capable of producing liquid oxygen while gaseous oxygen is delivered to the patient (personal communication, Thomas Petty, 1999). This system may be many years from general clinical use, but does demonstrate the ongoing innovation in this area.

A number of groups have also developed or are developing systems connecting the home unit to the home care company or physician by telemetry.<sup>13</sup> Information regarding the operation of the equipment, compliance with the prescription, and need for preventive maintenance can easily be provided. In addition, information about the patient's clinical status could be made available. Although there are problems with pulse oximetry, continued innovation in this technology may make oximeters suitable for periodic telemetric monitoring of patients in the home. In addition, heart rate, respiratory rate, and breath sounds could be made available via telemetry. It can be expected that over the next 10 years considerable innovation in the area of home oxygen delivery systems will be introduced,

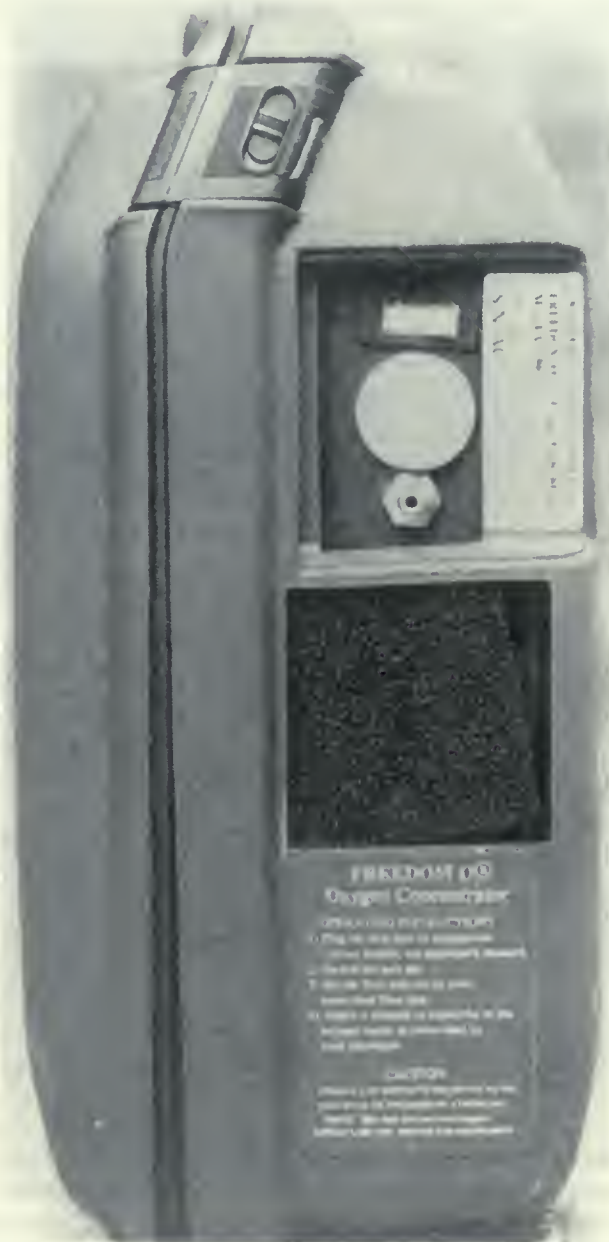


Fig. 10. Portable oxygen concentrator. (From Reference 1, with permission.)

since the number of patients at home on LTOT therapy is increasing. At this meeting, it was estimated by Patrick Dunne and Thomas Petty that about 750,000–1 million Americans currently receive home oxygen therapy.

### Summary

Table 5 summarizes my current perspective on home oxygen delivery systems in the United States. As I already indicated, scoring for cost and labor may be very different in other countries. As noted, all things considered, today



Fig. 11. Oxygen concentrator capable of transfilling an oxygen cylinder. (Courtesy of Invacare, Elyria, Ohio.)

Table 5. Comparison of Home Oxygen Therapy Delivery Systems

|                             | Cylinder | Liquid Oxygen | Concentrator |
|-----------------------------|----------|---------------|--------------|
| F <sub>IO<sub>2</sub></sub> | +++      | +++           | +            |
| Liter flow                  | +++      | ++            | +            |
| Portability                 | ++       | +++           | +            |
| Labor requirements          | +        | ++            | +++          |
| Cost                        | +        | +             | +++          |
| Innovation                  | +        | ++            | +++          |
| Ease of use                 | ++       | +             | +++          |
| Hazard potential            | ++       | +             | +++          |
| Total score                 | 15       | 15            | 18           |

+++ Highest, most favorable score

+ Lowest, least favorable score

the most reasonable system for home oxygen therapy is the concentrator. Problems with F<sub>IO<sub>2</sub></sub>, liter flow, and portability are clearly overshadowed by cost, labor, ease of use, and lack of potential hazard, as well as potential for

future innovation. I would expect with future development that the concentrator will score higher on F<sub>IO<sub>2</sub></sub>, liter flow, and portability. As a result of the anticipated large number of patients worldwide expected to require home oxygen therapy, ongoing improvement in this technology will be evident in the next few years.

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## Discussion

**MacIntyre:** How dangerous are tank or liquid oxygen systems? Do they ever fall over and have connectors break off, or do the liquids ever explode? Are there any fires?

**Kacmarek:** If you go back to the literature of the 1960s and 1970s reporting instances where tanks fell, at that time huge regulators were used, and if

they fell with enough force, the top of the cylinder was reported to break off. The cylinder acted like a torpedo and could go through a wall. Although I do not know of any recent report of this problem, it is clearly a possibility.

**MacIntyre:** There are no reports of people in the home having these things.

**Kacmarek:** I don't know of any recent reports. Do any of you know of a

liquid oxygen system in the home exploding?

**O'Donohue:** Trucks mostly—one that burned and caused a nearby house fire.

**Kacmarek:** OK. What happened?

**O'Donohue:** Recently, a truck that was transporting liquid oxygen and was possibly leaking oxygen or may

not have had the oxygen system properly closed was involved in a fire that destroyed a nearby home.

**Kacmarek:** This was a home delivery truck?

**O'Donohue:** Yes, a liquid oxygen delivery truck.

**Kacmarek:** Theoretically, the same thing could happen to delivery trucks going to the hospital, the large liquid oxygen trucks.

**McLellan:** That has happened more with large delivery vehicles where an individual has gotten into a vehicle after it has been sitting for a period of time. You know, liquid oxygen has a tendency to evaporate; they call that a normal evaporation time. Lighting a cigarette upon entering the vehicle is somewhat of a contraindication.

**Kacmarek:** Wasn't there a situation in Boston where an oxygen truck caught on fire? I believe I heard it on the news. But as far as problems in patients' homes, I do not know of any recent reports, or within a hospital setting, for that matter.

**McLellan:** We occasionally receive cannulas that have been burned. Generally, the problem is on the last second or third drag of a cigarette, when it becomes very short, toward the end of the nasal cannula is when it begins to melt. The only difference between a liquid oxygen system and a concentrator is that the pressure at which air exits a liquid is a little bit higher than when it comes out of a concentrator, and it serves as a fuse. The cannula serves as more of a fuse coming from a liquid oxygen system versus a cannula. It burns quicker coming from a liquid system. But as far as it actually entering the device and exploding, that has never happened.

**Kacmarek:** But you are relaying a user problem. That isn't an equipment

problem—no malfunctioning of the equipment. This is clearly an avoidable problem.

**Dunne:** Nice overview, Bob. However, an important point that you might consider in your summary slide is the ease of use of a concentrator by the medically naive user or caregiver. I would argue that the ease of use of the concentrator probably warrants a few more pluses. However, I do have a more provocative question. For about two or three years now the buzz with concentrators has been that some type of oxygen-sensing technology should be included as a standard feature. Do you have any thoughts about whether or not that should be mandated?

**Kacmarek:** As you know, most companies who make concentrators do have oxygen-sensing devices that can be an option. It seems to me a useful option, but does the problem of inadequate  $F_{IO_2}$  still exist? I ask the manufacturers (perhaps they'd like to comment) how likely with today's systems is failure to produce the target  $F_{IO_2}$ ? Clearly, if filters are not changed and they clog and you cannot draw in room air at the appropriate rate, the efficiency of the concentrator is decreased considerably. However, I'm led to believe that the efficiency of operations of today's concentrators is much better than it was 20 years ago and that the problems that we saw then are not problems that exist now on a regular basis. But I'd ask people who know better than me to comment.

**McLellan:** Excellent material. In regard to the telemonitoring, several manufacturers are obviously moving forward with projects to telemonitor liquid as well as concentrator devices. Do you see any issues that might occur in the future as a result of monitoring? Is the physician going to be liable if he knowingly is aware of a patient who does not use oxygen in the home? I mean, what sort of implications is this going to have, perhaps,

down the road? When a home care provider obviously knowingly continues to bill for oxygen therapy in those patients not using it.

**Kacmarek:** That same problem exists today. If the therapist going into the home knows that a patient has been ordered oxygen therapy for the last 6 months or a year, and the concentrator is always in the closet and obviously is not being used, and that patient is being continuously charged, it is a clear case of fraud as far as I'm concerned. I'm sure it will be considered fraud and abuse in the future, even more so if you have specific data to imply that this patient is simply *not* utilizing the device. Now, the liability issue—I really don't have any idea how that would come into play. As you talk to patients and discuss their compliance with most anything that is ordered, it is nowhere near the level of compliance that anybody would expect from a given patient. Every time you put some type of device on equipment that will truly tell you how frequently patients use devices, you're always surprised at how infrequently patients do, in fact, use it.

**Zielinski:** I also have a question about telemonitoring. I heard that some years ago in Japan they tried to monitor the use of oxygen concentrators from a central station, and also of patients' oxygenation during oxygen breathing using pulse oximetry. Do you, or anybody else, know the results of that trial?

**Kacmarek:** I do not.

**Wedzicha:** Nothing on that one, no. I don't have any results; sorry.

**Pierson:** In our planning for this conference, Tom and I wanted very much to have a participant from Japan, and we thought the presentation we would most like to hear from them was exactly on what you mentioned. A com-

pany there has had prototypes on trial in patients' homes that electronically monitor, through the phone line, the use of oxygen by the patient, which means the data could be collected and evaluated in some simple fashion. From our discussions, it appears that these devices are still in the prototype stage and that they do not yet have data that can be shared with us in a forum like this.

**Wedzicha:** Can I ask you about settings on the oxygen concentrator? You always start at 2 L/min. However, we very often have the need, because of hypercapnia in chest wall disease in neuromuscular patients, to use 1 L/min of oxygen therapy with a concentrator. Occasionally, we go to their homes and monitor patients on oxygen, and very often find the concentrators are not actually delivering 1 L/min or the equivalent. What settings do you recommend, and are regular checks done on the lower flow rates in concentrators?

**Kacmarek:** That's really a question for the oxygen therapy companies in the United States. I would assume that a device that was designed to provide oxygen flow from 1 L/min up to whatever was the maximum flow would accurately deliver that flow. My understanding is that most of these de-

vices will give you *reasonably* accurate flow at less than 1 L/min. Also, if you've ever taken a typical flow meter that's used in the hospital and measured the flow that is provided, you will find that one liter does not equal one liter. There is a certain level of error in all these devices, because they are not precision laboratory instruments. A 20% error is not unusual. As far as the frequency with which companies go into the home, it really depends on the type of oxygen therapy the patient is receiving. Those patients on a liquid oxygen system—personal visits on a 1 to 2 per week basis. As I said, with a 40-liter system, the 2-L/min flow will last approximately 11 days. Patients who have concentrators, much less frequent; the preventive maintenance may call for someone to come in monthly, and in some cases every 2 months to reassess the system or change the filter. So it becomes less frequent the more reliable the system.

**Stoller:** Although the subject of our discussion is home oxygen, I can't resist the temptation to discuss some of the shortcomings of hospital central supply systems. We recently became interested in this because we've been examining the adequacy—or lack

thereof—of the oxygen central supply and backup systems. This led to our conducting a survey of hospitals in Columbus and Cleveland, Ohio. We contacted by phone people and physicians who know the hospital oxygen systems and asked about mishaps in their hospitals. Of course, the literature contains some anecdotal reports of terrible mishaps in cutting lines, putting argon gas into the bulk vessel, and so on. I would submit that the same hazards that exist in the home, with a surprising and alarming frequency, occur in hospital central supply systems.

**Kacmarek:** Just as a final comment, I would agree with Jamie. Fifteen years ago when I came to Massachusetts General Hospital, we had similar types of problems. Every time we went to repair or expand the piping system, we never were sure of the effect of cutting a line. Gas from air could be fed into an oxygen line by a malfunctioning ventilator. Clearly, those types of problems have existed in the past, but most of us have focused on cleaning them up in the hospital. The older the building, the bigger was the problem.

**Stoller:** Because it will require big expenditures of resources to fix this, we call this the "O<sub>2</sub>K" problem.

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# Oxygen-Conserving Techniques and Devices

Robert McCoy RRT

## Introduction

## History of Oxygen Conservation

## Upper Airways Anatomy

## Breathing Patterns

## Options for Continuous-Flow Oxygen Conservation

## Intermittent-Flow Oxygen Conservation

## The Fallacy of Equivalency

## Using Oxygen-Conserving Devices

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## Economics of Oxygen Conservation

## Summary

[Respir Care 2000;45(1):95–103] *Key words: oxygen conservation, continuous flow, transtracheal oxygen, reservoir cannula, intermittent flow, demand flow, equivalency.*

## Introduction

Everyone breathes intermittently, why provide oxygen continuously?

Historically, oxygen has been given continuously because of the simplicity of the technique. Low-flow oxygen delivery to stable hypoxic patients started in the hospital, where oxygen distribution was not an issue, patients were on oxygen until they recovered, and then discharged. The cost of oxygen gas and delivery of oxygen within the hospital were not a concern, so options for lightweight, long-lasting, cost-effective technology were not investigated. With the movement toward a less expensive mode of health care, many patients have been discharged to home with long-term oxygen therapy (LTOT). Now, cost, availability, and capability of oxygen delivery systems are topics of debate for clinicians, providers, and payers of LTOT. Devices are being developed to improve the efficiency and effectiveness of oxygen therapy. Oxygen conservation has the potential to improve therapy, but must be monitored to ensure that patients are properly oxygenated at various activity levels. Saving oxygen without

meeting the patient's needs does not reduce cost, and defeats the purpose of LTOT.

## History of Oxygen Conservation

Dr Shapiro identified the problem with oxygen therapy years ago, stating that "Although blood gas measurements give us the means of properly monitoring oxygen therapy, and advances in respiratory therapy have made it possible to administer oxygen properly, few physicians or allied health personnel thoroughly understand oxygen therapy".<sup>1</sup>

Dr Cotes first described an oxygen-conserving system; it required the patient to manually activate a control valve connected to the oxygen tubing leading to the face mask.<sup>2</sup> Dr Heimlich first described transtracheal catheters in 1982, explaining the effectiveness of transtracheal delivery of low-flow oxygen.<sup>3</sup> This technique improved the efficiency of oxygen delivery by adding to the anatomical reservoir and reducing the flow requirements while maintaining adequate oxygen saturation. Reservoir cannulae were introduced in 1983, with the same objectives.<sup>4–6</sup> Both of these techniques were effective, but are used infrequently in LTOT. Electronically-controlled intermittent-flow devices were introduced in 1984, with a conserving device built into a liquid oxygen (LOX) portable.<sup>7</sup> This type of device senses the patient's inspiratory effort, delivers oxygen during inspiration, and stops the flow of oxygen during ex-

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halation. Even though intermittent-flow oxygen was technically feasible, it was rarely used.<sup>8</sup>

Prior to 1986, the Health Care Financing Administration (HCFA) reimbursed home oxygen providers for the amount of oxygen provided in packaged gas systems such as LOX and compressed gas cylinders, so there was financial incentive to provide as much oxygen as possible, which stimulated the growth of LOX systems. LOX systems provided excellent ambulatory oxygen for active patients, but increased the cost to distributors of home oxygen therapy because of the need to refill systems and the associated delivery costs. In 1986 HCFA introduced the 6-point plan that created a prospective payment for LTOT. This "modality neutral" approach changed the incentive for home oxygen providers, which started a move to lower the costs of operation, to control expense. LOX system availability declined. After several consensus conferences on LTOT,<sup>9</sup> LOX made a slight comeback because physicians were encouraging patients to be mobile, technology had improved, and there was increased competition from home medical equipment suppliers.

In 1998 HCFA again reduced the amount of reimbursement for LTOT by 25%, and then by another 5% in 1999. The challenge to provide a lightweight ambulatory oxygen system without the cost associated with LOX focused attention on oxygen-conserving technology and lightweight cylinders. In 1994 it was estimated that there were 18,000 oxygen-conserving devices (OCDs) used in home care.<sup>10</sup> In 1998 alone, approximately 80,000 OCDs were sold in the United States.<sup>11</sup>

Clinical studies have indicated that each of the conserving techniques are effective,<sup>8</sup> but intermittent flow has evolved as the technique of choice. The various intermittent-flow devices operate differently and should be tested at all activity levels for each patient. Most studies end with the comment that more long-term studies should be conducted,<sup>12</sup> but no long-term study has been done on intermittent-flow devices. "Reliable oxygen therapy becomes a matter of methodology and thorough understanding of oxygen delivery systems".<sup>1</sup>

Economics is driving the rapid growth of the OCD market, and clinicians are using products that have not had long-term clinical evaluations. OCDs are thought to be commodity products, but there are differences among the products, which need to be understood (Table 1),<sup>11</sup> and clinicians, patients, and home medical equipment suppliers have various misunderstandings about oxygen conservation (Table 2).

### Upper Airways Anatomy

It is important to understand the factors that affect oxygen delivery and dilution. The upper airways, breathing patterns, and oxygen flow affect the fraction of inspired

oxygen ( $F_{IO_2}$ ) (Fig. 1). Changes in breathing patterns can vary oxygen delivery. Consider the following example of a normal breathing pattern: tidal volume ( $V_T$ ) 500 mL,  $V_T$  useful (2/3 of  $V_T$ ) 350 mL,  $V_T$  dead space (1/3 of  $V_T$ ) 150 mL, dead space time 0.5 seconds, respiratory rate 20 per minute, inspiratory time 1 second, expiratory time 2 seconds, anatomic reservoir 50 mL, end-expiratory pause 0.5 seconds. To calculate  $F_{IO_2}$  of 2 L/min flow delivered to this person, we use the following formula:

$$2 \text{ L/min} = 33 \text{ mL/s (2000 mL/60s)}$$

17 mL of 100% oxygen from the anatomic reservoir

$$(0.5 \text{ s end-expiratory pause} \times 33 \text{ mL/s})$$

17 mL of 100% oxygen during inspiration

$$(0.5 \text{ s } T_{i\text{-}T_{\text{dead}}} \times 33 \text{ mL/s})$$

316 mL of 21% oxygen (room air)

$$= 66 \text{ mL of 100% oxygen}$$

$$17 + 17 + 66 = 100 \text{ mL 100% oxygen}$$

$$F_{IO_2} = 100 \text{ mL oxygen} / 350 \text{ mL V}_{\text{useful}} = 28\%$$

With the above assumptions on  $V_T$ , respiratory rate and inspiratory time, Table 3 shows the expected  $F_{IO_2}$  at flow rates of 1–6 L/min. Of course, if any of the assumptions change, the  $F_{IO_2}$  will also change.

### Breathing Patterns

#### Timing

"Timing is important when using a conserving device."<sup>13</sup> Gas inhaled in the first half of inspiration is delivered to the alveoli; gas inhaled in the second half of inspiration occupies dead space. Thus, the earlier the delivery of oxygen, the more likely the oxygen will reach the alveoli (Fig. 2).

#### Pooling

Higher  $F_{IO_2}$  delivered by continuous-flow oxygen (CFO) at the lower respiratory frequency is explained by the presence of the anatomic reservoir of the upper airways, allowing pooling of oxygen from the end of the last exhalation. Pooling also occurs with reservoir cannulas and transtracheal delivery of oxygen.

#### Dilution

With increasing respiratory rate, inspiratory time shortens and minute ventilation increases, diluting the oxygen

Table 1. Comparison of Oxygen Delivery Devices

| Device                              | Advantages                                           | Disadvantages                                                    | Issues                                                                                       |
|-------------------------------------|------------------------------------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Continuous flow (set appropriately) | No equipment required                                | Patient must set flow for activity level                         | This has always been a possibility, yet rarely done                                          |
| Transtacheal delivery               | Improved compliance with therapy<br>Patient benefits | Surgical procedure<br>No reimbursement for replacement catheters | Reimbursement would make this therapy more available                                         |
| Reservoir cannula                   | Simple to use<br>Low Cost                            | Esthetics                                                        | Proper education would improve utilization                                                   |
| Intermittent flow device            | Readily available<br>Simple to use                   | Wide variation of performance<br>Cost of batteries               | Misunderstanding of performance difference<br>Perception of equivalency with continuous flow |

Table 2. Concerns Associated with Oxygen Conservation

|                                 |                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Physician                       | <ul style="list-style-type: none"> <li>• There have been no long-term clinical studies of intermittent-flow OCDs.</li> <li>• Home medical equipment supplier might set up an OCD without informing the physician.</li> <li>• There has been positive experience with some devices and negative experience with others.</li> </ul>                      |
| Patient                         | <ul style="list-style-type: none"> <li>• Availability: many patients do not have access to devices (though they may learn about availability at lung clubs).</li> <li>• Ease of use: some devices are complicated to operate.</li> <li>• Training and education: patients need to know when a device is operating correctly or incorrectly.</li> </ul> |
| Home Medical Equipment Supplier | <ul style="list-style-type: none"> <li>• There is no reimbursement for an OCD.</li> <li>• Price and performance vary among devices; little information available on which product is the best value.</li> </ul>                                                                                                                                        |

OCD = oxygen-conserving device.

dose from CFO. Room air mixes with oxygen, causing a lower  $F_{IO_2}$ .

### Pulse Systems

Pulse systems (described further below) deliver oxygen early in the inspiratory effort, giving more oxygen in the effective portion of the breath so that more oxygen is delivered to the alveoli. Timing affects pulse systems, but pulse systems do not appear to be affected by dilution because of the early delivery of oxygen during inspiration.

### Demand Systems

Demand flow is delivered through the entire inspiratory section of the breath. Demand system flow rates are not as high as with pulse systems, so the volume of oxygen delivered per breath to the alveoli is less. Demand systems are affected by timing and dilution.

### Options for Continuous-Flow Oxygen Conservation

#### Titrate to the Lowest Continuous-Flow Delivery Per Activity Level

"Continuous low-flow systems are used because of tradition, familiarity, patient comfort, economics, and avail-

Table 3. Expected Fraction of Inspired Oxygen

| 100% Oxygen Flow Rate | $F_{IO_2}$ (%) |
|-----------------------|----------------|
| 1 L/min               | 24             |
| 2 L/min               | 28             |
| 3 L/min               | 32             |
| 4 L/min               | 36             |
| 5 L/min               | 40             |
| 6 L/min               | 44             |

$F_{IO_2}$  = fraction of inspired oxygen.  
(Modified, from Reference 1.)

ability—not because of accuracy or dependability."<sup>1</sup> In studies comparing demand oxygen delivery systems with CFO, the initial CFO setting might be titrated with little or no effort to optimize it. It is possible that in studies in which oxygen savings over CFO were reported, a small reduction in the CFO flow rate may have also realized oxygen savings without adverse effect on arterial oxygen saturation.<sup>11</sup>

Many patients who need supplemental oxygen are prescribed 2 L/min oxygen. This is a standard starting point for low-flow oxygen, more than meeting the patient's need. Oxygenation should be evaluated via blood gas analysis or

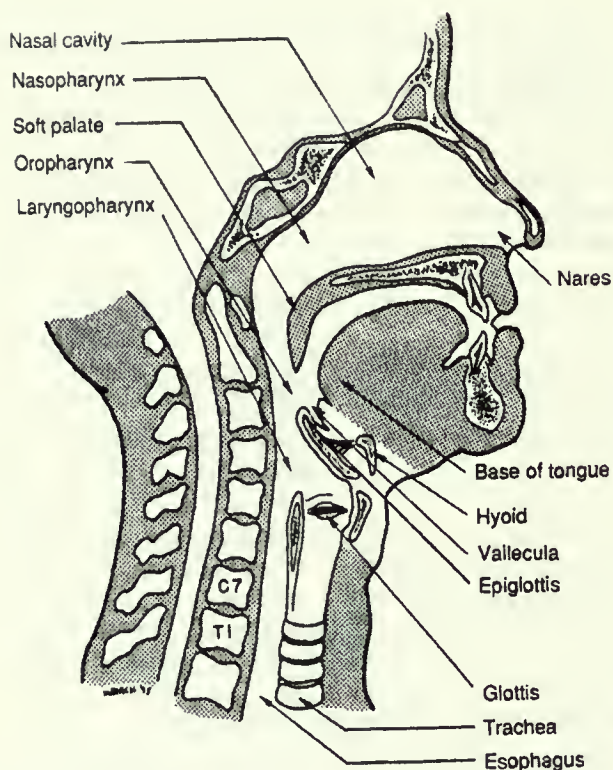


Fig. 1. Upper airways anatomy. The upper airways are ventilatory dead space. (From Caroline N, editor. *Emergency care in the streets*. Boston: Little, Brown. 1994. 63–112, with permission.)

oximetry for the lowest acceptable level of oxygen delivery for a given activity. A patient on 2 L/min might be properly oxygenated with only 1 L/min—a potential 50% savings. If this patient is on a home LOX system, a 50% reduction in delivery costs would also thus be achieved.

### Setting Up the Continuous-Flow System

- Monitor the patient's oxygen level at rest, exercise, and sleep, then write a prescription for each activity level.
- Educate the patient on the need to set the flow at the correct setting for each activity.
- Reinforce the different prescription flow rates with the analogy that different quantities of pills are necessary for different needs.

### Transtracheal Oxygen

Transtracheal oxygen devices are effective and have a lower flow requirement, which conserves oxygen (Fig. 3). The anatomical dead space acts as a reservoir, so flow can be reduced because there is increased pooling of oxygen between breaths. Advantages reported by patients include improved cosmetics (because the transtracheal system obviates the nasal cannula), reduced soreness on cheeks and ears (again, by virtue of eliminating the nasal cannula),

improved compliance with 24-hour therapy, and improved sense of taste and smell.<sup>14</sup> Transtracheal oxygen has been shown to work well with intermittent-flow devices, and these combine to improve compliance and reduce oxygen waste.<sup>15</sup>

### Setting Up the Transtracheal Oxygen System

- A transtracheal surgical procedure is performed by a qualified physician.
- Proper flows are prescribed for the various activity levels.
- The patient is instructed on the operation of the device and on changing and cleaning techniques.

### Reservoir Devices

Reservoir devices add a 20-mL reservoir close to the airway. The pooling of gas between breaths allows a lower CFO setting to achieve the same  $F_{IO_2}$ .<sup>6</sup> Reservoir devices come with either a moustache-type or a pendant-type reservoir (Fig. 4). The moustache-type reservoir sits under the nose, which is cosmetically displeasing to some patients, and they do not want to use this device in public. The pendant-type reservoir hangs in front of the chest and is therefore less noticeable. There are slight differences, related to dilution of oxygen, between the moustache-type and the pendant-type reservoirs, and these differences must be understood if the patient uses the devices interchangeably. The reservoir devices are simple, safe, and effective. Patients may be instructed to use the devices when not in a public place. The reservoir cannula might improve availability and ease of use when traveling, be used as a back up system at home, or any time the patient is alone.

### Setting Up the Reservoir Device System

- Monitor the patient for proper oxygenation at expected activity levels and prescribe proper flows.
- Instruct the patient on proper use of the device, with cleaning as necessary or monthly.

### Intermittent-Flow Oxygen Conservation

There are many options for intermittent-flow OCDs (Fig. 5). This type of device has grown in popularity and there are many manufacturers. In 1984, when first introduced, the technology was used to increase the operating time and reduce the weight of a liquid oxygen ambulatory system. Providers were reimbursed for oxygen used, so there was little interest in conservation. Now, there is financial incentive for conservation, and home medical equipment suppliers see OCD use as an important means of maintaining profitability.

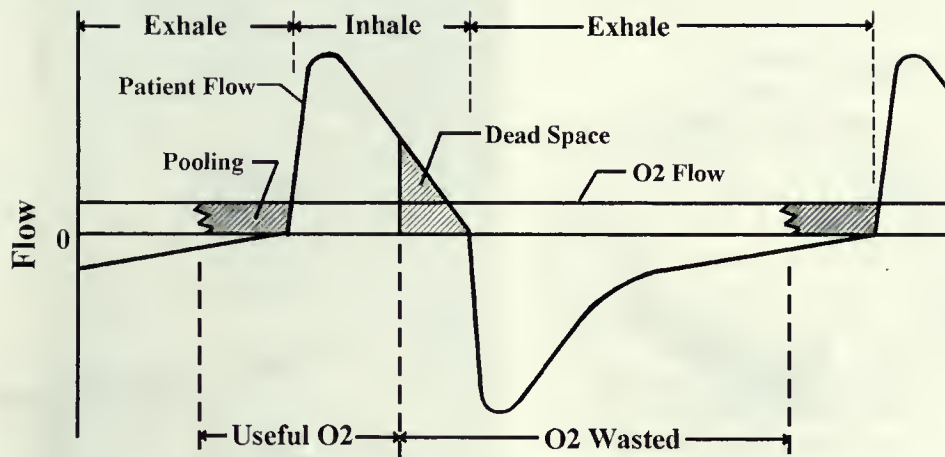


Fig. 2. A: Diagram of a respiratory flow cycle in relation to continuous-flow supplemental oxygen.

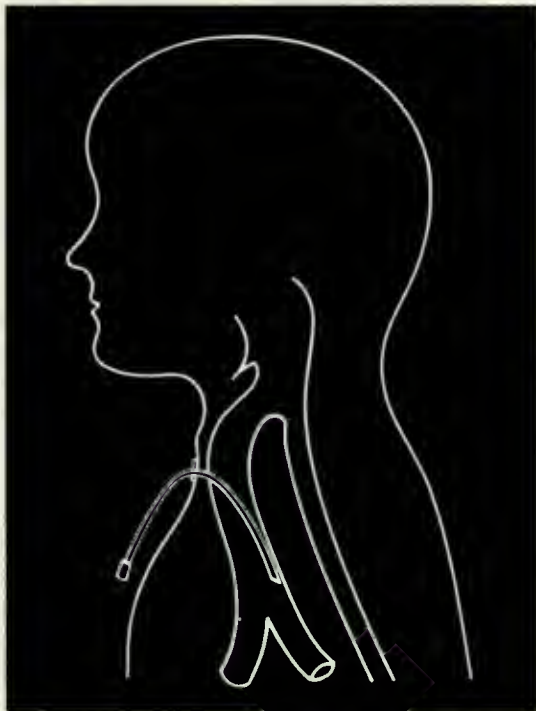


Fig. 3. Diagram of transtracheal catheter positioning.

Intermittent-flow OCDs are of three types: pulse, demand, and hybrid.<sup>11</sup> The difference between the types is how the oxygen flow is delivered (Fig. 6). With a pulse system, oxygen is delivered in a short burst at the beginning of the inspiratory cycle (at a flow rate higher than

CFO) and the oxygen shuts off prior to the end of the inspiratory cycle. A demand device delivers an equivalent flow to the corresponding CFO setting for most of the inspiratory cycle. A hybrid device uses a combination of the operating principles of the pulse and demand systems.

Intermittent-flow OCDs sense an inspiratory signal, which opens a valve to deliver oxygen. The device is either time-cycled or pressure-cycled. Flow and time are determined by the manufacturer, and devices vary in oxygen delivery. The devices are powered pneumatically or by batteries.

### The Fallacy of Equivalency

All of the OCD devices are stated to be "equivalent" to continuous flow. However, each manufacturer has a different concept of equivalency, and devices differ in volume delivered at the same flow setting (Fig. 7). While demand oxygen delivery systems may function similar to CFO under the assumed conditions, they may deviate from equivalence with other breathing patterns. Thus, clinical studies have shown demand oxygen delivery systems to produce similar results to CFO,<sup>16-20</sup> but there are studies that report differences.<sup>21-22</sup> Many factors affect equivalency, including  $V_T$ , frequency, anatomy, and expiratory flow.

Manufacturers could use volume settings rather than CFO equivalency for OCDs, which would allow clinicians to better understand the oxygen delivery and to compare devices. But OCD manufacturers have been hesitant to

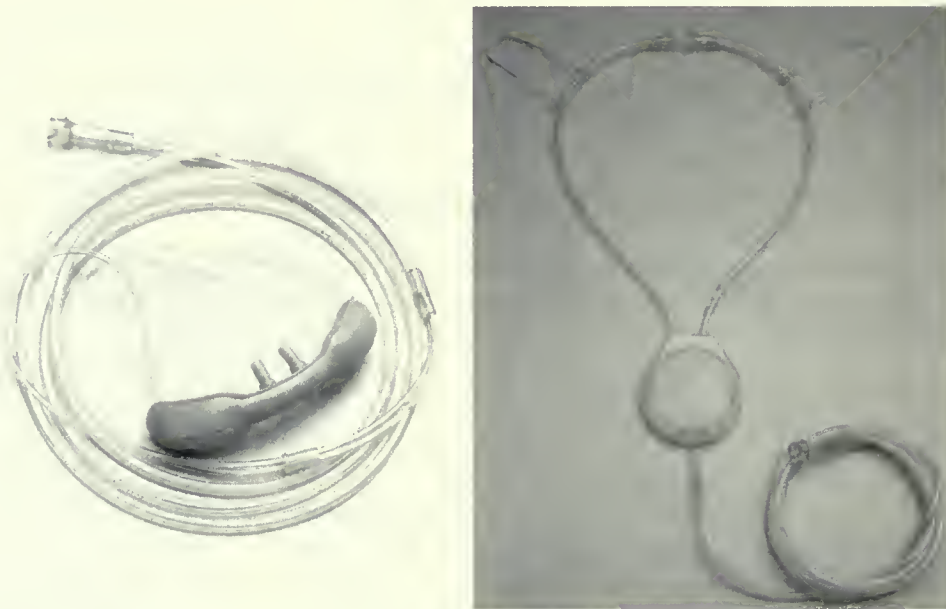


Fig. 4. Oxyimizer oxygen reservoir devices: moustache-type (left) and pendant-type (right). (Photographs courtesy of Chad Therapeutics.)



Fig. 5. Intermittent-flow oxygen-conserving devices. Front row (left to right): EX-3000 (DeVilbiss, Somerset, Pennsylvania), EX-2000 (DeVilbiss), Impulse Select (AirSep, Buffalo, New York), CR-50 (Mallinckrodt, St Louis, Missouri) OxiClip (Mallinckrodt). Back row (left to right): O<sub>2</sub>N Demand (Victor, Denton, Texas), O<sub>2</sub> Advantage (Western Medica, Westlake, Ohio), Venture (Invacare, Elyria, Ohio), DOC-2000 (Transtacheal Systems, Englewood, Colorado), Oxymatic 301 (Chad Therapeutics, Chatsworth, California).

change the flow settings on these devices for fear that this would be changing the prescription for LTOT; yet the equivalency setting has been shown to not be equivalent. If 2 L/min continuous flow was ordered, an OCD giving 33 mL of oxygen would give the clinician a better understanding of the volume of gas per breath and the differences and capabilities of the device. Settings for all low-flow oxygen delivery devices should be a reference point

and not an end point. Flows should be adjusted for the patient's needs and not left on one setting.

#### Using Oxygen-Conserving Devices

Titrate continuous flow correctly; this can be done in the hospital or home. Oximetry measurements during activity determine the appropriate prescription for a given

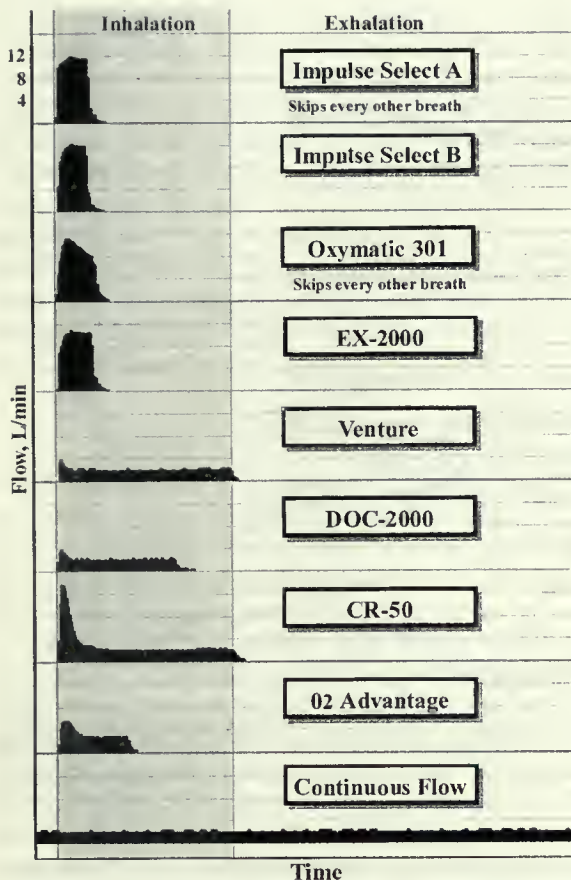


Fig. 6. Oxygen delivery flow profiles for selected oxygen delivery systems (measured at a setting of 2 L/min, respiratory rate of 20/min, and inspiratory-expiratory ratio of 1:2). (From Reference 11.)

activity level. The goal is to determine the proper setting for therapy, not the amount of oxygen that can be saved. All methods of oxygen conservation should save oxygen compared to CFO.

Choose the conserving technique. Each device has benefits that should be evaluated for each patient. The technique chosen should be explained to the patient. The clinician should know the capabilities and limitations of the device selected.

Monitor the patient with each device at different activity levels and adjust the oxygen setting appropriately.

Educate the patient on the proper operation of the device. Devices operate differently from each other and from CFO. If the patient feels the device is not working, check oxygen saturation. Some devices have alarms that indicate if an inspiratory signal has been missed, indicating a disconnected cannula or device malfunction.

Monitor operating duration of ambulatory systems. Respiratory rate affects operating duration, so the supply of oxygen should be checked frequently for the first few months of operation to determine the travel time of a portable and the required delivery schedule for replacement

cylinders. Flow rate and respiratory rate also affect battery life, so the patient should monitor battery life during the first few months of operation to determine operating times.

### Sensitivity and Sleep

Little attention has been given to the sensitivity of OCDs. This is an important issue related to when oxygen is delivered in the respiratory cycle. Devices that are slow to respond to an inspiratory signal will deliver oxygen late in the inspiratory cycle and thus be less effective. This will be important in the case of the weak inspiratory signal associated with shallow breathing and sleep. There have been very few clinical studies testing OCDs during sleep. One study indicated that inspiratory signal sensitivity should be set for each individual patient during sleep, which in that study resulted in excellent device response for sleeping patients.<sup>15</sup>

### New Systems

#### Oximetry-Driven Oxygen-Conserving Devices

A pulse-type OCD is currently being tested that adjusts the level of oxygen delivered based on an oximetry reading. This concept may eliminate the variability of oxygen delivery with existing systems. The first (unpublished) clinical study found better oxygenation than either CFO or a currently-available OCD. The device improved savings by reducing flow to the lowest acceptable setting and has the capability of stopping oxygen flow if oximetry indicates no oxygen is necessary. The reliability of the oximeter is an issue for this device because appropriate oxygen control depends on a correct oximetry reading. This device will cost more than traditional devices, but the oxygen savings will prove this product to have economic benefits. Historically, products that are not reimbursed by HCFA, even if clinically superior, do not fare well in the home care market. This product will need to be driven by clinicians if it is to be successful.

#### Concentrator Fills Cylinder

Chad Therapeutics (Chatsworth, California) and Invacare (Elyria, Ohio) have introduced systems that fill cylinders in the home from the output of an oxygen concentrator. Even though these systems do not require an OCD, patients can benefit from the use of smaller cylinders with an OCD with the home fill system.

#### Concentrator Fills Liquid Oxygen Portable

IN-X Corporation (Denver, Colorado) is developing a system to fill LOX portables from a concentrator. Again, an OCD is not required, but a small LOX portable with a

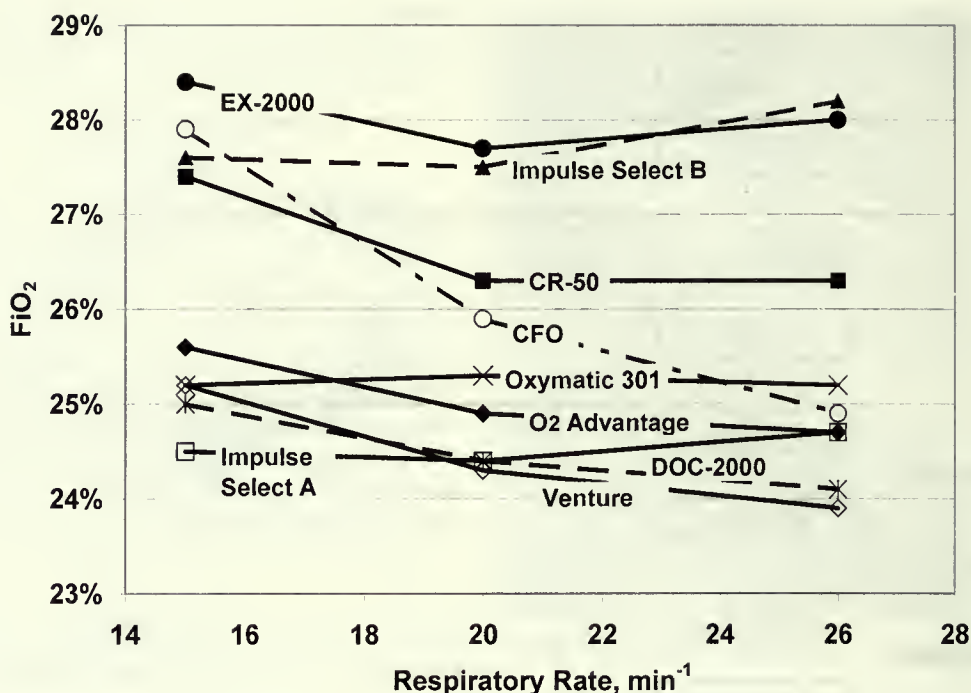


Fig. 7. Fraction of inspired oxygen ( $F_{IO_2}$ ) measured for demand oxygen delivery systems (model names and manufacturers as in Figure 5), in comparison with continuous-flow oxygen (CFO), during three breathing patterns. Both the continuous-flow oxygen and the demand oxygen delivery systems were set at 2 L/min. (From Reference 11.)

conserving device would be lighter and last longer than a CFO system.

### Portable Concentrator

Several manufacturers are developing portable concentrators. Such a device would require an OCD in order to reduce the size and weight of the system and thus make a 10-pound ambulatory concentrator possible.

### Nitric Oxide Delivery

OCDs can be used for other gas-delivery applications. Nitric oxide has been reported to be delivered via OCD, making ambulatory nitric oxide possible.<sup>23</sup>

### Economics of Oxygen Conservation

Oxygen gas is relatively inexpensive. Oxygen containers and packaging and delivering oxygen are the expensive components of home LTOT. CFO may waste 60–85% of the oxygen supplied to the patient. This waste requires more frequent filling of packaged gas systems (LOX and cylinders) and additional home deliveries. The use of an OCD reduces the number of deliveries or the number of cylinders required for an ambulatory patient. Consider these examples of potential oxygen savings. With a LOX system that has been receiving weekly deliveries at \$35 (estimat-

ednational average), installation of an OCD that provides 3:1 oxygen savings over a CFO system would eliminate 2 deliveries out of 3, a \$93 monthly savings. Likewise, a system that uses 6 E-size cylinders per week and requires weekly deliveries at \$35 would, if installed with a 3:1 savings OCD, require 2 out of 3 fewer deliveries (again, a savings of \$93/mo).

### Current Situation

Intermittent-flow OCDs are being used on cylinders as an ambulatory source. LOX capital investment costs and delivery costs are perceived to be too expensive, so home-medical equipment suppliers prefer cylinders for ambulatory patients and concentrators for stationary oxygen. To be competitive, home medical equipment suppliers must provide ambulatory systems, but, because OCDs are not reimbursed, some home medical equipment suppliers look for the OCD that offers the greatest oxygen savings at the lowest cost, which could negatively affect patient oxygenation. The lack of understanding of OCDs and the rapid growth of this market are creating confusion as to the operation, effectiveness, safety, and application of OCDs.

### The Future of Oxygen-Conserving Devices

More manufacturers are bringing new OCDs to market, which is similar to the rapid growth of oxygen concentra-

tors in the mid-1980s. There are approximately 12 OCD manufacturers in the United States, with 3 of these having 70% of the market. Foreign manufacturers are developing products and looking at the United States as a growing market and a potential for expanding their market. The OCD market should continue to grow for the next 5 years because of reimbursement cuts in LTOT and the shift to cylinders as the preferred ambulatory modality. OCDs will become better understood, and appropriate prescribing for LTOT will evolve through experience and education. Prices will drop and features will improve, as has happened with most products used in home care.

### Summary

OCDs are available and their use is growing in the home care market because of economic factors associated with LTOT, but this trend has evolved with little clinical research. There is great variability among the oxygen control systems, and physicians need to test patients on each device, at each activity level the patient is capable of in the home, and to write a prescription for each activity level. OCDs should be used because of the patient benefits of improved activity and compliance with a 24-hour prescription, and the economic benefit associated with reduced delivery of oxygen. Clinicians and patients need to be thoroughly familiar with the oxygen system they are using and to understand its capabilities and limitations. More research is required to evaluate the application and effectiveness of and the differences between products and outcomes of OCDs used in home care. Equivalency between CFO and OCDs should not be necessary because of the differences between these delivery methods and the great variability of products.

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## Discussion

**Spratt:**\* One real concern I have here, and I think both presenters did a great job, but it's very interesting that when we've looked at oxygen therapy, we've looked at it entirely in terms of a technology, and we've really not addressed it as a level of care. I find it very interesting that at an American Association for Respiratory Care-sponsored event, we've spent very little time talking about the care that needs to go along with this technology, and as the technology increases, what's going to happen is that the cost to deliver care is going to come down. Reimbursement is going to continue to come down with that, and as that happens, care is going to come down with it. I think as a clinical community, it is contingent upon us to address that issue and talk about the care that needs to go with the technology, and the need for education, the need for proper titration, and the need to monitor and assess the patient. All of these are issues that are very important to oxygen care in the home and, really, we've spent very little time discussing them.

**Dunne:** In somewhat of a different vein, I think Bob has raised the bar in terms of the importance of having physicians prescribe oxygen-conserving devices appropriately, and essentially reject the perception that oxygen conserving technology is the same for all devices currently available. I find the diverse technology absolutely increasing the responsibilities of the home care providers, especially in the selection of the device to be used and the manner by which titration occurs. So I don't think we're abrogating the patient care component as much as we are illuminating some of the practices

that have become ingrained strictly because of opinion or poorly-thought-out processes. I have one other comment. In addition to the prescription for the portable system and for the stationary system, the Joint Commission now requires a separate and distinct prescription when an oxygen conserving device is being used. They obviously recognize that a lot of oxygen-conserving technology probably has not been used in the most appropriate manner.

**O'Donohue:** At a time when we're talking about more physician involvement, we have to realize that the new HCFA Form 484 takes away the prescribing possibility for the physician so that a prescription must be written separately from that form; as Pat has implied, maybe even multiple prescriptions. But certainly HCFA and Medicare have not made it easier for the physician. I would also like to reiterate your point about the conserving devices. Two liters is not equivalent to two liters from one delivery system to another, but there are still significant savings from the use of oxygen conserving devices. Every patient needs to be titrated as to the dose that they need, not only at rest but also with exercise, because there are marked differences between rest and exercise oxygen flows needed to correct hypoxemia with many of the conserving devices that are much greater than they are with continuous flow by nasal cannula.

**Johnson:**\* What I see lacking in this industry, at least, is that there's really no standard. You can't compare it to continuous flow and there's no one device that has stood out, really, above any others to prove that they're functional for patients in all settings and all conditions.

**McCoy:** I agree. The standard is something that if we had an American Society for Testing and Materials standard for oxygen conservation, everyone would be following that, but right now, whoever is the market leader is followed. I think how that happened was that the patents are driving the development of technology. If someone owns a patent and another company comes out with a device, they can't copy that unless they license it. So they have to come up with something that's different to have a device that doesn't infringe on existing patent.

**Johnson:** I'd like to say also that in talking with dealers of durable medical equipment, they're the ones who are driving which device is used—not the doctors, at all.

**McCoy:** Right. I agree with that.

**Dunne:** I certainly agree with what was said earlier, but I think what this Journal conference will do is to strengthen the link between the clinical application of oxygen conserving technology and the oxygen requirements of the patients. You mentioned the shake-out in the market that's going to occur much like concentrator technology did 10 years ago, where there were a dozen or so different manufacturers, and I believe there are 5 left today. The same is probably going to happen with oxygen conserving devices. Hopefully, what will happen is that the devices that really do offer the best flexibility in terms of meeting the patient's individual needs will survive. At least I hope that's what we'll see.

**McCoy:** That's only if clinicians get involved, because price is driving the market right now. I've surveyed home care companies, and the number one issue, when you ask how they decide which conserving device to buy, is price. That's the first thing they say.

\*Greg Spratt, Rotech Medical Corporation, Kirksville, Missouri.

\*Robert Johnson MD, Salter Labs, Arvin, California.

# Effects of Long-Term Oxygen Therapy on Mortality and Morbidity

Gerard J Criner MD

## Introduction

### Effect of Long-Term Oxygen Therapy on Mortality

#### British Medical Research Council Long-Term Domiciliary Oxygen Therapy Trial

#### Nocturnal Oxygen Therapy Trial

### Effect of Long-Term Oxygen Therapy on Pulmonary Hemodynamics

### Effect of Long-Term Oxygen Therapy on Sleep

### Effect of Long-Term Oxygen Therapy on Exercise Performance

## Summary

[Respir Care 2000;45(1):105–118] *Key words: oxygen therapy, mortality, morbidity, long-term oxygen therapy, hypoxemia, sleep hypoxemia exercise hypoxemia.*

## Introduction

Since the introduction of oxygen as a therapeutic agent 70 years ago, much has been learned regarding the detrimental effects of hypoxemia and the beneficial impact of oxygen therapy on reversing hypoxemia's complications in patients with advanced lung disease. It is projected that there are close to 800,000 patients receiving long-term oxygen therapy (LTOT) in the United States, at a cost of approximately \$1.8 billion annually.<sup>1</sup> The large numbers of patients receiving supplemental oxygen as treatment and the high costs incurred in providing oxygen therapy necessitate the practitioner to be knowledgeable of the effects of LTOT on patient morbidity and mortality. This review will examine the effects of LTOT on patient survival, pulmonary hemodynamics, sleep, and exercise capacity.

### Effect of Long-Term Oxygen Therapy on Mortality

Untreated hypoxemia often progresses to tissue hypoxia, which may result in irreversible adverse effects on

vital organ function. The prognosis of patients in whom hypoxemia leads to the development of cor pulmonale portends a poor prognosis, with mortality ranging anywhere from 32% to 100%.<sup>2,3</sup> Early noncontrolled studies showed a reduction in mortality in patients with chronic obstructive pulmonary disease (COPD), cor pulmonale, and severe hypoxemia with the use of continuous oxygen therapy for 7–41 months.<sup>4</sup> Two landmark studies performed in the late 1970s, the Nocturnal Oxygen Therapy Trial (NOTT) and the British Medical Research Council (MRC) Domiciliary Study, examined the effects of LTOT on survival and physiologic function in patients with severe chronic bronchitis and emphysema.

### British Medical Research Council Long-Term Domiciliary Oxygen Therapy Trial

The British Medical Research Council Long-Term Domiciliary Oxygen Therapy Trial was conducted in the late 1970s and reported in March of 1981.<sup>5</sup> It was carried out in 3 centers in the United Kingdom and enrolled 87 patients, all under the age of 70 years, who had chronic bronchitis or emphysema with irreversible airways obstruction (forced expiratory volume in the first second [FEV<sub>1</sub>] range 0.58–0.75 L), severe hypoxemia (arterial oxygen tension [P<sub>aO<sub>2</sub></sub>] range 49.4–51.8 mm Hg), carbon dioxide retention (arterial carbon dioxide tension [P<sub>aCO<sub>2</sub></sub>] range 56–60 mm Hg), and a history of cor pulmonale (mean

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pulmonary artery pressure range 32.3–35.0 mm Hg). Patients randomized to receive oxygen were given 2 L/min via nasal prongs for at least 15 hours a day.

Patients in both groups had similar baseline physiologic data. In 5 years of survival follow-up, 19 of the 42 oxygen-treated patients died, compared to 30 out of 45 control subjects who did not receive oxygen and died. A survival advantage emerged in the 66 men entered into the trial, but not until 500 days had elapsed into the trial. A survival difference in the female population was also greater in the oxygen-treated subjects compared to the controls but was identified earlier in the follow-up period, with 8 of 12 female control patients dying within 3 years of the trial. Mortality appeared to be highest in the subgroup of patients who had the highest elevations in baseline  $P_{aCO_2}$  and red cell mass.

Although mortality was favorably affected by long-term oxygen use, time spent in the hospital because of exacerbations of respiratory failure and work attendance were not affected. The rate of change in physiologic variables in those subjects who survived over 500 days was recorded annually. There were no statistically significant differences between patients treated with oxygen and those treated without oxygen in the rate of decrease of  $FEV_1$  or  $P_{aO_2}$ , or increase in  $P_{aCO_2}$ , red cell mass, or pulmonary artery pressures. However, there appeared to be a trend that LTOT prevented a progressive decrease in  $P_{aO_2}$  and in the rate of increase in pulmonary vascular resistance without provoking a further increase in  $P_{aCO_2}$ . Note, however, that those patients having repeated studies followed for  $\geq 500$  days reflected only half of the total patients enrolled into the trial (ie, 22 patients treated with oxygen and 18 patients not receiving oxygen therapy).

## Nocturnal Oxygen Therapy Trial

The NOTT study, sponsored by the National Heart, Lung, & Blood Institute, reported in 1980 findings on continuous versus nocturnal oxygen therapy in hypoxemic COPD patients.<sup>6</sup> This multicenter ( $n = 6$ ) study enrolled 203 patients with hypoxemic COPD who were randomly allocated to receive either continuous oxygen therapy or 12 hours of nocturnal oxygen therapy. All subjects were followed for at least 12 months to determine the effects of oxygen therapy on survival, pulmonary vascular pressures, neuropsychological function, and quality of life. Inclusion and exclusion criteria for the NOTT are shown in Table 1.

Of the 1,043 patients recruited and screened for the trial, only 203 patients fulfilled eligibility criteria. Of the patients screened but excluded from the trial, 31% were found to have other major disease, 15% refused, 12% were previously treated with LTOT, and in 21% of subjects  $P_{aO_2}$  increased after optimization of medical therapy during the 3-week period of pre-enrollment stabilization. Baseline characteristics of the enrolled patients showed that they were elderly (mean age 65 years), 80% were male, and mean  $P_{aO_2}$  was 50.8–51.5 mm Hg, with moderately severe airways obstruction ( $FEV_1$  29% of predicted). In addition, baseline hematocrit was 47% of predicted, with a mean pulmonary artery pressure of 29–30 mm Hg. Patients were eucapnic in both groups ( $P_{aCO_2}$  43.4–43.9 mm Hg).

Compliance was assessed in the study both by use of timers on the oxygen source and examining patient logs. In patients randomized to nocturnal oxygen therapy only, both timer and patient log data were congruent, indicating that 82% of the nocturnal oxygen therapy patients used oxygen 13 h/d or less. In contrast, patients randomized to continuous oxygen therapy averaged 17.7 h/d, according to the

Table 1. Inclusion and Exclusion Criteria for the Nocturnal Oxygen Therapy Trial

| Inclusion Criteria                                  | Exclusion Criteria                                                                             |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------|
| Clinical diagnosis of COPD                          | Previous oxygen therapy: 12 h/d for 30 days prior to 2 months                                  |
| Hypoxemia                                           | Other diseases that may influence mortality, morbidity, compliance, or ability to give consent |
| $P_{aO_2} \leq 55$ mm Hg                            |                                                                                                |
| $P_{aO_2} \leq 59$ mm Hg plus one of the following: |                                                                                                |
| • edema                                             |                                                                                                |
| • hematocrit $\geq 55\%$                            |                                                                                                |
| • P pulmonale on electrocardiogram                  |                                                                                                |
| Lung function                                       |                                                                                                |
| $FEV_1/FVC < 70\%$ post bronchodilator              |                                                                                                |
| $TLC \geq 80\%$ of predicted                        |                                                                                                |
| Age $> 35$ years                                    |                                                                                                |

COPD = chronic obstructive pulmonary disease.  $P_{aO_2}$  = arterial oxygen tension.  $FEV_1/FVC$  = ratio of forced expiratory volume in the first second to forced vital capacity. TLC = total lung capacity.

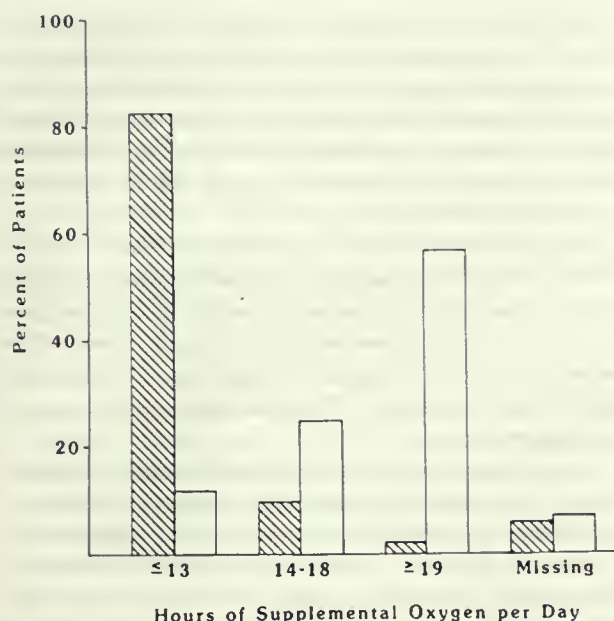


Fig. 1. Compliance with treatment regimens as assessed by patient log expressed as frequency distribution of daily oxygen use in the Nocturnal Oxygen Therapy Trial. Patients on nocturnal oxygen therapy are represented by the hatched bars and patients on continuous oxygen therapy are represented by the open bars. "Missing" indicates patients with incomplete data. (From Reference 6, with permission.)

timers. Compliance with the assigned treatment arm is shown in Figure 1.

Mortality in the 203 patients was followed for an average of 19.3 months. Eighty nocturnal oxygen and 87 con-

tinuous oxygen therapy subjects were followed for 12 months, whereas 29 nocturnal oxygen and 37 continuous oxygen therapy patients were followed for 24 months. A total of 64 subjects died in the trial, 41 subjects in the nocturnal oxygen therapy group and 23 subjects in the continuous oxygen therapy group. Overall mortality of the subjects assigned to continuous oxygen therapy and nocturnal oxygen therapy over 3 years of observation is shown in Figure 2. Twelve-month mortality in the nocturnal oxygen therapy group was 20.6%, versus 11.9% in the continuous oxygen therapy group, and 24-month mortality in the nocturnal oxygen therapy group was 40.8%, versus 22.4% in the continuous oxygen treatment group.

At all 6 centers, mortality for the nocturnal oxygen therapy group exceeded that for the continuous oxygen therapy group. Mortality further examined in subgroups of patients with  $P_{aCO_2} > 43$  mm Hg, lower pH, and higher levels of mood disturbance such as depression and anxiety, showed statistically significantly lower mortality in those treated with continuous versus nocturnal oxygen therapy. Although patients treated with continuous oxygen therapy were hospitalized less, and had fewer hospital days than nocturnally treated patients, these differences were not statistically significant.

When the effect of continuous versus nocturnal therapy was assessed for its impact on physiologic variables, no significant changes were found in arterial blood gas values, lung volumes, FEV<sub>1</sub>, maximum work attained, mean pulmonary artery pressures, or cardiac index. However, hematocrit values were more reduced in patients on continuous oxygen therapy than those randomized to noctur-

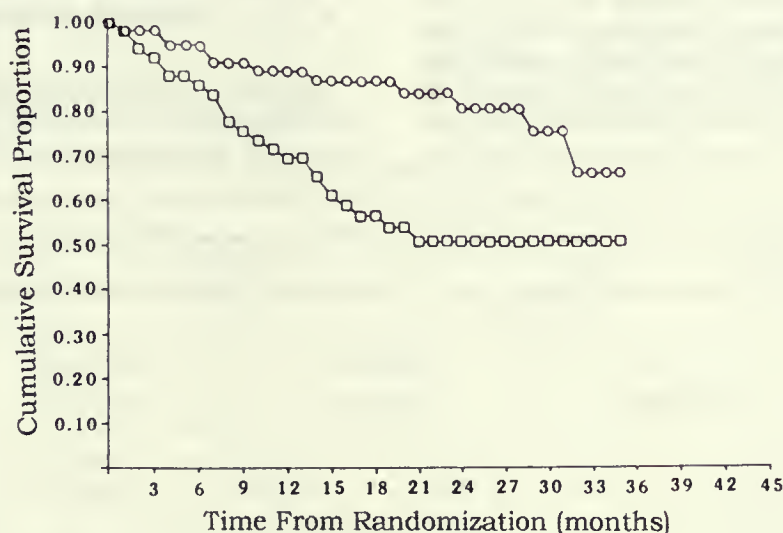


Fig. 2. Overall mortality in the patients enrolled in the National Oxygen Treatment Trial. Circles (upper curve) represent continuous oxygen therapy group. Squares (lower curve) represent nocturnal oxygen therapy group. Twelve-month mortality in the nocturnal oxygen group was 20.6%, versus 11.9% in the continuous oxygen therapy group. Twenty-four-month mortality in the nocturnal oxygen group was 40.8%, versus 22.4% in the continuous oxygen treatment group. (From Reference 6, with permission.)

Table 2. Comparison of British Medical Research Council (MRC) and Nocturnal Oxygen Therapy Trial (NOTT) Long-Term Oxygen Treatment Trials

|                                      | MRC                                | NOTT                        |
|--------------------------------------|------------------------------------|-----------------------------|
| <i>n</i>                             | 87                                 | 203                         |
| Study design                         | Prospective, controlled            | Prospective, controlled     |
| Protocol                             | No O <sub>2</sub> vs nocturnal use | Nocturnal vs continuous use |
| FEV <sub>1</sub>                     | 0.58–0.76 L                        | 29% of predicted            |
| Percent female                       | 24                                 | 20–23                       |
| P <sub>aO<sub>2</sub></sub> (mm Hg)  | 49–51                              | 51                          |
| P <sub>aCO<sub>2</sub></sub> (mm Hg) | 55–60                              | 43                          |
| mPaP (mm Hg)                         | 32–35                              | 30                          |
| Hrs O <sub>2</sub> use/day           | 0 vs 15                            | 12 ± 2.5 vs 17.7 ± 4.8      |
| Smoking status                       | 25–52%                             | ?                           |

FEV<sub>1</sub> = forced expiratory volume in the first secondP<sub>aO<sub>2</sub></sub> = arterial oxygen tensionP<sub>aCO<sub>2</sub></sub> = arterial carbon dioxide tension

mPaP = mean pulmonary artery pressure

nal treatment (approximately 7% difference), as was pulmonary vascular resistance (17.6% greater decrease in pulmonary vascular resistance found in the group receiving continuous vs nocturnal therapy).

It should be recognized that although both of the above studies showed improved survival, patients were not comparable between studies (Table 2). Patients in the MRC study tended to be more ill and with more evidence of resting hypercapnia and cor pulmonale. Furthermore, patients in the MRC study had a significant number of participants who continued to smoke even after enrollment into the trial (27% in the control group and 44% in the placebo group), whereas no comment was made on the incidence of continued smoking on patients enrolled into the NOTT. Finally, the MRC study found no statistically significant impact of nocturnal oxygen therapy versus no oxygen treatment on physiologic variables, whereas, the

NOTT study found a statistically significantly greater decrease in pulmonary vascular resistance and hematocrit associated with continuous oxygen therapy (Table 3). The causal relationship of a reduction in hematocrit and pulmonary vascular resistance on influencing survival, whether using continuous or nocturnal oxygen therapy, was not established, however.

Despite the difference in the above-referenced studies, these 2 prospective and controlled trials appear to establish that nocturnal oxygen therapy is better than no oxygen therapy at all, and continuous oxygen therapy is better than nocturnal oxygen therapy in severely hypoxemic patients with elevated hematocrit, pulmonary artery pressure, and respiratory acidosis.

In an attempt to extend the above findings to patients who suffer from less severe disease and only moderate hypoxemia, Gorecka et al<sup>7</sup> evaluated 135 patients (P<sub>aO<sub>2</sub></sub> 56–65 mm Hg at rest) with advanced air flow obstruction (FEV<sub>1</sub> 0.83 L) who were randomly allocated to receive no oxygen therapy (*n* = 67) or LTOT (*n* = 68). Patients assigned to either group were followed every 3 months for at least 3 years. The cumulative survival rates for the group at large were 88% at 1 year, 77% at 2 years, and 66% at 3 years. The authors found no significant difference in survival rates between the 2 patient groups treated with LTOT versus control therapy. Patients who were younger and had better spirometric values and higher body mass index showed better survival. This was similar to the findings of Neff and Petty,<sup>4</sup> who found no survival benefit in COPD patients given supplemental oxygen when severe hypoxemia or cor pulmonale was not present.

### Effect of Long-Term Oxygen Therapy on Pulmonary Hemodynamics

Substantial evidence suggests that the presence of secondary pulmonary hypertension in COPD patients increases the risk for hospitalization<sup>8</sup> and is associated with wors-

Table 3. Comparison of Outcomes in the British Medical Research Council (MRC) and Nocturnal Oxygen Therapy Trial (NOTT) Long-Term Oxygen Treatment Trials

|                              | MRC          |                          | NOTT                     |                           |
|------------------------------|--------------|--------------------------|--------------------------|---------------------------|
|                              | Control      | Nocturnal O <sub>2</sub> | Nocturnal O <sub>2</sub> | Continuous O <sub>2</sub> |
| Mortality                    | 29%/y (risk) | 12%/y* (risk)            | 40.8%/2 y                | 22.4%/2 y*                |
| Spirometry                   | ↓            | ----                     | ----                     | ----                      |
| PVR                          | ↑            | ↓                        | ↓ 6.5%                   | ↓ 11.1%*                  |
| RBC mass or HCT              | ↑            | ↓                        | ↓ 2.0%                   | ↓ 9.2%*                   |
| P <sub>aCO<sub>2</sub></sub> | ↑            | ↓                        | ----                     | ----                      |
| P <sub>aO<sub>2</sub></sub>  | ↓            | ---- or ↑                | ----                     | ----                      |

\*Statistically significant

PVR = pulmonary vascular resistance. RBC = red blood cell. HCT = hematocrit. P<sub>aCO<sub>2</sub></sub> = arterial carbon dioxide tension. P<sub>aO<sub>2</sub></sub> = arterial oxygen tension.

ened survival.<sup>9-11</sup> Because of the known association of resting hypoxemia with the development of secondary pulmonary hypertension, investigators have focused on supplemental oxygen as treatment for pulmonary artery hypertension in patients with pulmonary hypertension and hypoxemic COPD. Indeed, earlier noncontrolled studies had shown that the continuous administration of oxygen for 4-8 weeks had beneficial effects on reducing resting pulmonary artery pressures.<sup>12,13</sup> Moreover, both the MRC study and the NOTT study examined the effects of supplemental oxygen on pulmonary hemodynamics.

In the MRC study, rates of change in pulmonary hemodynamics were calculated for 23 men treated  $\geq 15$  hours a day with 2 L/min supplemental oxygen and compared to 21 control men not treated with oxygen who survived  $> 500$  days. Although no significant differences were found in pulmonary vascular resistance between the groups, it was found that pulmonary vascular resistance increased much more in the control men not treated with oxygen than it did in the men treated with supplemental oxygen.

In a subsequent publication, the NOTT group defined hemodynamic abnormalities in patients with severe, stable hypoxemic COPD and compared changes in the hemodynamic patterns of patients given nocturnal oxygen therapy to those receiving continuous oxygen therapy. They also described the response in hemodynamic variables to exercise and the effects of acute oxygen inhalation on these variables. Finally, they made correlations between hemodynamic findings and survival.<sup>14</sup>

Right heart catheterization was performed 3 weeks after observation, when patients were stable outpatients without oxygen therapy. Baseline hemodynamic measurements were made while patients breathed room air oxygen for a 15-minute rest period and then during cycling exercise. Measurements of pulmonary hemodynamics were then repeated at rest and during exercise after 30 minutes of supplemental oxygen inhalation. Following baseline cath-

eterization, patients were randomized to outpatient treatment of either nocturnal oxygen therapy for 12 hours a day or continuous oxygen therapy. Both groups were then followed for an average of 32 months. Repeat cardiac catheterization was performed in both groups 6 months after treatment.

Table 4 shows baseline and mean acute changes in hemodynamic values after oxygen administration in stable hypoxemic COPD patients. Measured and derived hemodynamic variables at baseline showed a moderate degree of resting pulmonary hypertension, with a moderate elevation in pulmonary vascular resistance. Stroke volume as well as mean cardiac index was reduced, with an elevation in right ventricular stroke work index. Resting mean levels of pulmonary artery pressure had a significant inverse correlation with  $P_{aO_2}$  ( $r = -0.28$ ,  $p < 0.01$ ) and mean sleep arterial oxygen saturation ( $S_{aO_2}$ ) ( $r = -0.4$ ,  $p < 0.001$ ), and significant positive correlation with  $P_{aCO_2}$  ( $r = 0.24$ ,  $p < 0.01$ ). As shown in Table 4, exercise while breathing room air led to small but statistically significant increases in cardiac index, stroke volume index, and pulmonary vascular resistance, as well as increases in mean pulmonary artery pressure, mean right atrial pressure, pulmonary artery occlusion, and right ventricular stroke work index.

Table 4 shows the effects of breathing oxygen for 30 minutes during rest and during exercise. At rest, breathing oxygen was associated with a reduction in cardiac index, stroke volume index, right ventricular stroke work index, and mean pulmonary artery pressure. Similarly, exercise done while breathing oxygen was associated with reduction in mean right atrial pressure, mean pulmonary artery pressure, mean pulmonary artery occlusion pressure, pulmonary vascular resistance, and right ventricular stroke work index, compared with exercise performed by chronic stable COPD patients breathing room air. However, the effects of breathing oxygen (in contrast to breathing room

Table 4. Baseline and Mean Acute Changes in Hemodynamic Values in Stable Hypoxemic COPD Patients

|                                  | Air            |                | O <sub>2</sub> |               | Change          |                 |
|----------------------------------|----------------|----------------|----------------|---------------|-----------------|-----------------|
|                                  | Rest           | Exercise       | Rest           | Exercise      | Rest            | Exercise        |
| mRaP (mm Hg)                     | 5 $\pm$ 3      | 13 $\pm$ 6*    | 6 $\pm$ 3      | 12 $\pm$ 6    | 0 $\pm$ 2       | -1 $\pm$ 4*     |
| mPaP (mm Hg)                     | 29 $\pm$ 10    | 50 $\pm$ 16*   | 28 $\pm$ 10    | 45 $\pm$ 14   | -1 $\pm$ 4†     | -4 $\pm$ 7†     |
| PaOP (mm Hg)                     | 9 $\pm$ 5      | 18 $\pm$ 8*    | 10 $\pm$ 6     | 17 $\pm$ 9    | 0 $\pm$ 4       | -2 $\pm$ 6†     |
| CI (L/min m <sup>2</sup> )       | 2.9 $\pm$ 0.6  | 4.1 $\pm$ 0.9* | 2.8 $\pm$ 0.6  | 4 $\pm$ 0.8   | -0.1 $\pm$ 0.4† | -1 $\pm$ -0.5   |
| SVI                              | 34 $\pm$ 7.4   | 38 $\pm$ 8*    | 32 $\pm$ 7.3   | 38 $\pm$ 8    | -2 $\pm$ 5.5†   | -0.2 $\pm$ -4.7 |
| PVR (dyn-s-cm <sup>-5</sup> )    | 330 $\pm$ 164  | 367 $\pm$ 182* | 323 $\pm$ 174  | 337 $\pm$ 161 | 0.7 $\pm$ 98.9  | -24 $\pm$ 102†  |
| RVSWI (g-m/beat-m <sup>2</sup> ) | 17.2 $\pm$ 8.2 | 31 $\pm$ 11.5* | 16.1 $\pm$ 7.4 | 29 $\pm$ 11   | -1.5 $\pm$ 4†   | -2.0 $\pm$ 6.1† |

\* $p < 0.001$  compared to rest

† $p < 0.01$  comparing air to O<sub>2</sub>

COPD = chronic obstructive pulmonary disease. mRaP = mean right arterial pressure. mPaP = mean pulmonary artery pressure. PaOP = pulmonary artery occlusion pressure. CI = cardiac index. SVI = stroke volume index. PVR = pulmonary vascular resistance. RVSWI = right ventricular stroke work index.

(Modified, from Reference 14.)

# EFFECTS OF LONG-TERM OXYGEN THERAPY ON MORTALITY AND MORBIDITY

Table 5. Chronic Changes in Hemodynamic Values in COPD Patients After 6 Months of Treatment\*

|                                  | NOT           |                | COT         |             |
|----------------------------------|---------------|----------------|-------------|-------------|
|                                  | Rest          | Exercise       | Rest        | Exercise    |
| mRaP (mm Hg)                     | 0 ± 3         | 0 ± 6          | 0 ± 3       | -2 ± 7      |
| mPaP (mm Hg)                     | 0 ± 7         | -4 ± 13†       | -3 ± 1†     | -6 ± 14‡    |
| PaOP (mm Hg)                     | 0 ± 5         | -1 ± 9         | 0 ± 5       | 1 ± 10      |
| CI (L/min m <sup>2</sup> )       | 0.1 ± 0.7     | 0.1 ± 0.8      | 0.1 ± 0.7   | 0.3 ± 1.3   |
| SVI                              | 0 ± 8.4       | 2.3 ± 8.5†     | 2.4 ± 8.1†  | 4.3 ± 9.8‡  |
| PVR (dyn-s-cm <sup>-5</sup> )    | -15.4 ± 116.9 | -47.9 ± 117.8† | -67.9 ± 174 | -107 ± 190‡ |
| RVSWI (g-m/beat-m <sup>2</sup> ) | -0.1 ± 5.8    | -2.2 ± 9.7     | -0.7 ± 7.3  | 4.0 ± 14.8  |

\*Measured breathing room air

†p < 0.05

‡p < 0.01

COPD = chronic obstructive pulmonary disease. NOT = nocturnal oxygen therapy. COT = continuous oxygen therapy. mRaP = mean right arterial pressure, mPaP = mean pulmonary artery pressure. PaOP = pulmonary artery occlusion pressure. CI = cardiac index. SVI = stroke volume index. PVR = pulmonary vascular resistance. RVSWI = right ventricular stroke work index. (Modified, from Reference 14.)

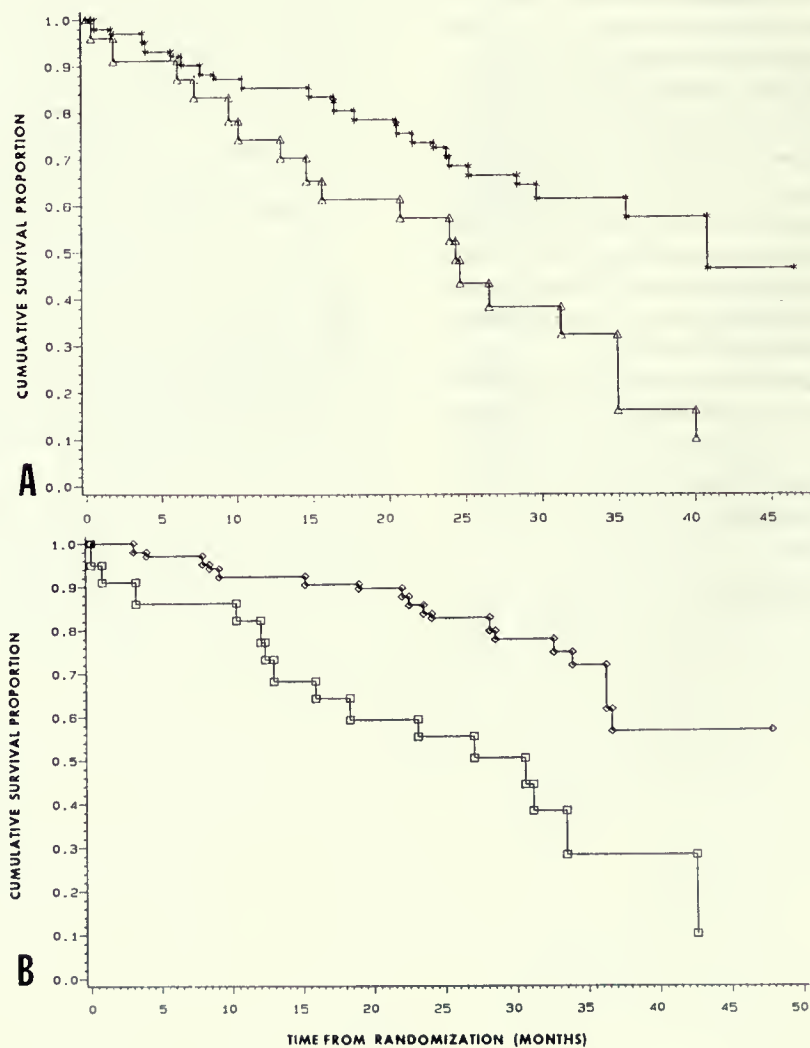


Fig. 3. A: Patients receiving nocturnal oxygen therapy. Patients are divided into those with baseline pulmonary vascular resistance < 400 dyn-s-cm<sup>-5</sup> (asterisks, upper curve) and those with baseline pulmonary vascular resistance > 400 dyn-s-cm<sup>-5</sup> (triangles, lower curve). B: Patients receiving continuous oxygen therapy. The patients are divided into those with baseline stroke volume index > 3 (diamonds, upper curve) and those with baseline stroke volume index < 3 (squares, lower curve). (From Reference 14, with permission.)

air) on hemodynamic variables were minimal both at rest and during exercise.

Table 5 shows chronic changes in hemodynamic values in COPD patients after 6 months of nocturnal or continuous oxygen therapy. Six-month follow-up data were not available for 61 of 179 patients who underwent initial right heart catheterization, because they had either died, were too ill, refused follow-up catheterization, or had incomplete data. However, the 118 patients who had follow-up 6-month cardiac catheterization had baseline characteristics that were identical to the baseline characteristics of those who had no follow-up data ( $n = 85$ ).

The use of nocturnal therapy was associated with significant decreases in mean pulmonary artery pressure and pulmonary vascular resistance during exercise, but the changes in resting and exercising pulmonary vascular resistance were more statistically significant in those who used continuous oxygen therapy. Patients given continuous oxygen therapy also showed significant improvements in exercise mean pulmonary artery pressure and stroke volume index (Table 5). However, absolute differences in hemodynamic changes between the nocturnal and continuous oxygen therapy groups were not statistically significant. In subsequent analysis, patients that had  $> 25\%$  improvement in resting or exercise pulmonary vascular resistance after treatment were considered to be oxygen responders, whereas those with  $\leq 5\%$  improvement in pulmonary vascular resistance were considered nonresponders to oxygen. When baseline data were compared between oxygen responders and nonresponders as defined above, the only variable that suggested a marginally significant difference was baseline awake  $S_{aO_2}$ .

As shown in Figure 3, among the 7 hemodynamic variables measured at baseline, only pulmonary vascular resistance was associated with improved survival in patients given nocturnal oxygen therapy, whereas stroke volume index was associated with improved survival in those receiving continuous oxygen therapy.

Although this study showed that pulmonary hemodynamics at rest and with exercise might be favorably influenced by the use of supplemental oxygen in stable, chronically hypoxemic COPD patients, the changes in pulmonary hemodynamics were small. Although changes in pulmonary vascular resistance or stroke work index were seen as baseline parameters associated with reduced mortality in those given nocturnal or continuous oxygen therapy, respectively, and suggest that a hemodynamic effect of oxygen therapy was responsible for the survival difference between these two therapies, this supposition was not demonstrated by this study. In addition, the study was somewhat limited because catheterization was only performed 6 months after therapy. Catheterization performed later after treatment may have identified more substantial changes in the magnitude of the effects of supplemental oxygen. De-

spite these limitations, however, the study appears to show that hemodynamic deterioration during 6 months of oxygen therapy, whether given continuously or nocturnally, was avoided.

Three subsequent studies have examined the effect of oxygen on the pulmonary circulation and have attempted to determine (1) whether the effect of LTOT on pulmonary hypertension is maintained longer than 6 months, (2) whether the acute effect of oxygen administration on pulmonary artery pressure predicts survival in hypoxemic COPD patients treated with LTOT, and (3) the effect of acute withdrawal of supplemental oxygen on pulmonary artery pressures in COPD patients.

Weitzenblum<sup>15</sup> studied 16 patients with severe COPD ( $FEV_1 0.89 \pm 0.28$  L) who were hypoxemic ( $P_{aO_2} 50.2 \pm 6.6$  mm Hg), and moderately hypercapnic ( $P_{aCO_2} 51 \pm 6.4$  mm Hg) by conducting 3 consecutive right heart catheterizations in each patient. The first right heart catheterization was performed  $47 \pm 28$  months before the administration of LTOT. The second heart catheterization was performed immediately before the initiation of LTOT. A third right catheterization was performed  $31 \pm 19$  months after the administration of LTOT. Oxygen therapy was provided 15–18 h/d and prescribed at flows based on usual criteria. During the period between initial evaluation and initiation of supplemental oxygen,  $P_{aO_2}$  decreased from  $59.3 \pm 9.4$  mm Hg to  $50.2 \pm 6.6$  mm Hg and mean pulmonary artery pressure increased from  $23.3 \pm 6.8$  mm Hg to  $28.0 \pm 7.4$  mm Hg, ( $p < 0.005$ ). However, after long-term oxygen administration was initiated and subsequent follow-up at an average of  $1\frac{1}{2}$ –2 years later,  $P_{aO_2}$  was stable, and pulmonary artery pressure decreased from  $28.0 \pm 7.4$  mm Hg to  $23.9 \pm 6.6$  mm Hg, ( $p < 0.05$ ). Furthermore, pulmonary hypertension improved in 12 of 16 patients in whom there had been a yearly increase in mean pulmonary artery pressure of  $1.47 \pm 2.3$  mm Hg before the initiation of supplemental oxygen. Following the administration of supplemental oxygen, a yearly decrease in mean pulmonary artery pressure of  $2.15 \pm 4.4$  mm Hg was observed. These data were interpreted as showing that the effect of LTOT on pulmonary artery hypertension is maintained over the long term and extends the findings of the NOTT group that LTOT may favorably influence pulmonary hemodynamics for a period substantially greater than 6 months.

One of the limitations of the NOTT study was its inability to predict the effect of LTOT based on acute changes in pulmonary hemodynamics at rest while inspiring supplemental oxygen. Sliwinski<sup>16</sup> studied 46 patients with severe COPD who qualified for LTOT. Thirty-nine patients responded to acute administration of supplemental oxygen with a decrease in mean pulmonary artery pressure of  $\leq 5$  mm Hg and were called oxygen nonresponders. In 7 patients mean pulmonary artery pressure decreased  $> 5$  mm

Hg and they were labeled oxygen responders. Patients were then prescribed LTOT by conventional criteria for 2 years or until death. The 2-year survival rate was 69% in nonresponders and 50% in responders to the acute administration of supplemental oxygen. The authors concluded that survival of patients with severe COPD administered LTOT was not related to the acute effects of oxygen on pulmonary artery pressure and that significantly improved survival may be seen despite a lack of acute change in hemodynamic variables.

In order to determine whether the changes in pulmonary hemodynamics in patients receiving continuous versus nocturnal oxygen therapy are related to the daily duration of oxygen therapy, Selinger et al<sup>17</sup> made serial measurements in 20 stable hypoxemic COPD patients during supplemental oxygen therapy and then after interrupting supplemental oxygen therapy. The authors found that removing oxygen produced a delayed increase in pulmonary vascular resistance, which required approximately 2.5 hours to develop. They found that pulmonary vascular resistance index increased by 31% during rest ( $8.14 \pm 0.61$  units vs  $6.23 \pm 0.51$  units,  $p < 0.01$ ) and by 29% during lower extremity cycling ( $8.11 \pm 0.9$  units vs  $6.31 \pm 0.7$  units,  $p < 0.001$ ). The increase in pulmonary vascular resistance occurred because of an increase in pulmonary artery pressure without corresponding changes in pulmonary capillary wedge pressure or cardiac index. These data appear to suggest that an interruption in oxygen supplementation for several hours a day in chronically stable hypoxemic COPD patients can result in an elevation of pulmonary artery pressures at rest and during exercise.

In summary, data from the above studies appear to show that inspiration of supplemental oxygen in hypoxemic COPD patients is associated with favorable but minimal changes in the magnitude of pulmonary hypertension at rest and during exercise. Furthermore, it tends to suggest that favorable changes in pulmonary hemodynamics secondary to oxygen supplementation are enhanced in the group of patients that receive oxygen continuously, compared to those who receive it on an intermittent daily basis. Improvements in survival of COPD patients receiving continuous versus nocturnal oxygen therapy are hard to attribute solely to changes in pulmonary hemodynamics based on the available data, nor does the response to acute administration of oxygen on pulmonary hemodynamics appear to predict the long-term effects of oxygen therapy on survival. Further studies are required to determine the causal relationship of oxygen supplementation on pulmonary hemodynamics and survival, and to predict which subgroups of patients with pulmonary hypertension and hypoxemic COPD are more likely to benefit from long-term administration.

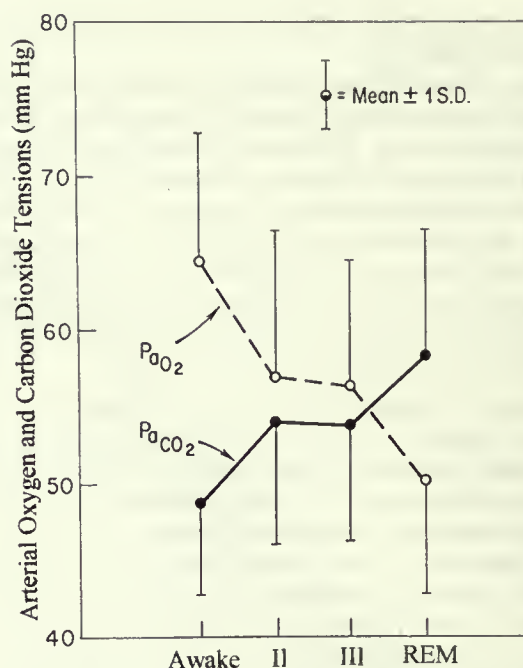


Fig. 4. Mean arterial oxygen tension ( $P_{aO_2}$ ) and arterial carbon dioxide tension ( $P_{aCO_2}$ ) in 8 patients with severe stable COPD.  $P_{aO_2}$  decreases during sleep Stages II and III, and decreases further during rapid-eye-movement (REM) sleep. Conversely,  $P_{aCO_2}$  increases during Stages II and III, and increases further during REM sleep. (From Reference 18, with permission.)

### Effect of Long-Term Oxygen Therapy on Sleep

Approximately 25 years ago, Koo et al<sup>18</sup> first measured arterial blood gas tensions in sleeping COPD patients. They found that in 8 men with severe COPD ( $FEV_1 < 1.7$  L),  $P_{aO_2}$  decreased from a mean of 64 mm Hg while awake to 58 mm Hg during non-rapid-eye-movement (REM) sleep, and decreased further to 50 mm Hg in REM sleep.  $P_{aCO_2}$  increased from 48 mm Hg while awake to 52 mm Hg during non-REM sleep, and to 58 mm Hg during REM sleep. Figure 4 shows mean  $P_{aO_2}$  and  $P_{aCO_2}$  during the various sleep stages. Similar results were reported by others, who also found that pulmonary artery pressure increased 20 mm Hg during REM sleep in patients with moderately severe COPD.<sup>19</sup>

Several mechanisms have been hypothesized for hypoxemia developing during sleep in patients with severe COPD. These include alveolar hypoventilation, abnormal ventilation-perfusion matching, and a reduction in functional residual capacity. Ventilation is reduced during all phases of sleep in normal subjects and COPD patients.<sup>20-23</sup> During non-REM sleep, decreases in ventilation are relatively small, but marked hypoventilation can occur during the more variable breathing periods of REM sleep.<sup>20</sup> Moreover, REM hypoventilation appears to be most severe during periods of intense eye movement.<sup>23</sup> The cause of REM

sleep-related hypoventilation has not been completely determined, but is thought to be related to altered brainstem function<sup>24</sup> and/or a marked diminution of hypoxic and hypercapnic ventilatory responses.<sup>25</sup> Finally, hypoventilation during REM and non-REM sleep has been thought to be in some part related to the increase in airways resistance that occurs during sleep.

Some authors have shown that a reduction in alveolar ventilation during REM sleep is insufficient to account for all of the hypoxemia observed in COPD patients and have suggested that ventilation-perfusion imbalance is an additional contributing factor to the REM sleep-associated hypoxemia found in severe COPD patients.<sup>26</sup> A decrease in functional residual capacity during REM sleep has been found in normal subjects and COPD patients,<sup>27</sup> which may contribute to sleep hypoxemia.

The consequences of sleep hypoxemia on pulmonary hemodynamics, sleep quality, and, ultimately, survival in COPD patients has been a subject of several studies. Fleetham et al<sup>28</sup> assessed the role of hypoxemia and sleep disruption in 24 COPD patients studied while breathing air and oxygen during sleep. The authors found that the lowest mean  $S_{aO_2}$  occurred during REM sleep and that patients spent 22.4% of the night with  $S_{aO_2} > 5\%$  below the awake  $S_{aO_2}$ . When compared with age-matched normal controls, sleep quality was poor in the severe COPD patients, as indicated by a decrease in total sleep time, a greater frequency of sleep state changes, and increased arousal frequency. However, these investigators found that oxygen therapy had no apparent effect on sleep quality. They believed their data suggested that hypoxemia itself was not responsible for precipitating poor sleep quality but an associated phenomenon such as hypercapnia may have been responsible for the increased arousal frequency.

In contrast, Calverley et al<sup>29</sup> found that supplemental oxygen may improve sleep quality in patients suffering chronic bronchitis or emphysema. They recorded full polysomnographic studies and  $S_{aO_2}$  in 20 sleeping patients with chronic bronchitis and emphysema. Thirteen patients had low  $P_{aO_2}$  and elevated  $P_{aCO_2}$ , and 7 patients had relatively normal  $P_{aO_2}$  and  $P_{aCO_2}$ . The patient group findings were compared to 9 healthy subjects of similar age, and both patient groups had lower stable  $S_{aO_2}$  than the normal subjects, but the patients with resting hypoxemia and hypercapnia had significantly more hypoxemic episodes during sleep, in contrast to the group of patients with relatively normal awake  $P_{aO_2}$  and  $P_{aCO_2}$ . However, in both the patients and the healthy subjects, transient nocturnal hypoxemia was most common during REM sleep, and its duration was not related to any sleep variable examined. In the 6 patients who had resting hypoxemia and hypercapnia and were studied while breathing supplemental oxygen, fewer hypoxemic episodes per night were found, along with an increase in the amount of proper sleep stages.

Intervening wakefulness and drowsiness were reduced by supplemental oxygen therapy and the amount of time spent in sleep increased 17% while inspiring oxygen, in contrast to while inspiring room air. The authors concluded that the differences in sleep quality were explained by the alleviation of nocturnal hypoxemia.

The presence of nocturnal oxyhemoglobin desaturation in COPD patients and its impact on pulmonary hemodynamics have been recently investigated by several authors. Fletcher et al<sup>30</sup> studied 152 COPD patients who had daytime  $P_{aO_2} \geq 60$  mm Hg, using full polysomnography to detect nonapneic nocturnal oxyhemoglobin desaturation. He found that 27% of patients desaturated below a baseline sleep saturation of 90% for  $\geq 5$  minutes, reaching a nadir oxyhemoglobin saturation of  $\geq 85\%$ . Demographic data, pulmonary function, and historical factors failed to separate those patients who desaturated from those who did not desaturate. Patients who desaturated, however, had a lower  $P_{aO_2}$  (69.8 mm Hg vs 75.5 mm Hg) and a higher  $P_{aCO_2}$  (41.2 mm Hg vs 38.2 mm Hg) during measurement of daytime awake arterial blood gases, than did nondesaturators.

Some authors have hypothesized that chronic nocturnal desaturation without daytime hypoxemia may lead to the development of pulmonary hypertension and cor pulmonale in COPD patients. Levi-Valensi et al<sup>31</sup> investigated the relationship between sleep variables and daytime pulmonary hemodynamics in 40 COPD patients with daytime  $P_{aO_2}$  of 60–70 mm Hg. Patients were defined as desaturators if they spent at least 30% of the recorded sleep time with a transcutaneously-measured  $S_{aO_2} < 90\%$ . In contrast to the findings of Fletcher et al,<sup>30</sup> described above, daytime arterial blood gases and pulmonary function studies could not distinguish between desaturators ( $n = 18$ ) and nondesaturators ( $n = 22$ ). Pulmonary artery mean pressure was higher in desaturators ( $19.1 \pm 4.7$  mm Hg vs  $16.9 \pm 1.9$  mm Hg,  $p < 0.05$ ). The pulmonary hypertension patients ( $n = 6$ ) were all desaturators, and differed from the other desaturators in having higher numbers of desaturation dips, longer durations of dips in arterial saturation, and lower mean nocturnal arterial oxygen saturation levels. The authors concluded that a causal relationship existed between nocturnal desaturation and the development of pulmonary hypertension.

In order to determine whether supplemental oxygen would improve cardiopulmonary hemodynamics in patients with episodic nocturnal desaturation, Fletcher et al<sup>32</sup> conducted a double-blind, randomized, 3-year trial of nocturnal supplemental oxygen for sleep desaturation in COPD patients at an outpatient chest clinic of a Veterans Administration medical center. The study included 51 patients with moderate to severe COPD and daytime  $P_{aO_2} \geq 60$  mm Hg. Thirty-eight subjects had proven REM-associated sleep desaturation and 13 subjects had no desaturation.

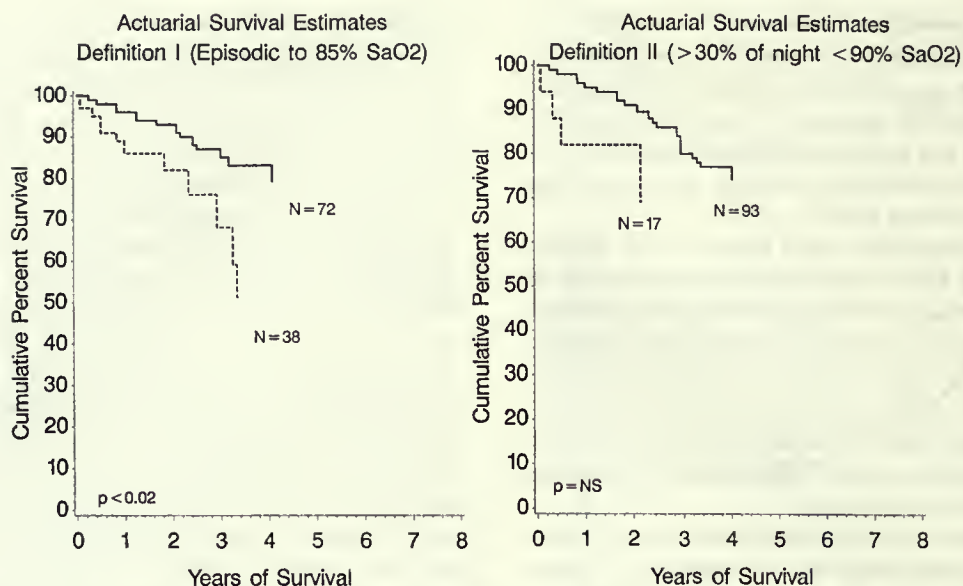


Fig. 5. Actuarial survival estimates in nocturnal desaturating (dashed line) versus nocturnal nondesaturating subjects (solid line) after oxygen-treated subjects were removed from the analysis. In the left panel, patients are separated into nocturnal desaturating and nocturnal nondesaturating groups based on the episodic occurrence of desaturation from a baseline sleep oxygen saturation ( $S_{aO_2}$ )  $> 90\%$  for 5 minutes or below  $85\%$ . In the right panel, patients are separated into nocturnal desaturating and nocturnal nondesaturating groups based on the definition of  $> 30\%$  of time spent in bed with  $S_{aO_2} < 90\%$ . (From Reference 33, with permission.)

Nocturnal oxygen at 3 L/min was delivered by oxygen concentrator to 19 desaturating subjects, and room air at 3 L/min was delivered by a sham concentrator to the remaining 19 desaturating subjects. The nocturnal desaturating group, who received supplemental oxygen during sleep over the course of 36 months, showed a significant downward trend in pulmonary artery pressure ( $-3.7$  mm Hg) compared with desaturating subjects treated with room air ( $+3.9$  mm Hg,  $p < 0.02$ ). However, there was no detectable difference between the groups in nonvascular parameters of hypoxemia such as hemoglobin and red blood cell mass. None of the nondesaturating subjects, but 11 of 38 desaturating subjects (6 sham and 5 treated with oxygen), died within the 3-year period of observation. Although there was a trend toward improved survival in desaturating patients who were prescribed supplemental oxygen, the difference between groups was not statistically significant.

In a follow-up study, the International Oxygen Club conducted an international multicenter trial examining the effect of supplemental oxygen on survival in COPD patients who had daytime  $P_{aO_2} > 60$  mm Hg, some subjects with and some without nocturnal oxyhemoglobin desaturation.<sup>33</sup> There was a trend toward increased survival in 35 oxygen-treated versus 38 oxygen-nontreated nocturnal desaturating subjects, but the difference was not statistically significant.

Based on the above data, continuous nocturnal oxygen therapy should be prescribed for patients who have  $P_{aO_2}$  values of  $\leq 55$  mm Hg during sleep, which is associated with hypoxic organ dysfunction.<sup>34</sup> In addition, it has been recommended that the untoward effect of nocturnal hy-

poxemia on organ dysfunction be documented to reverse with the use of oxygen. Data suggesting that oxygen therapy in patients who have daytime  $P_{aO_2} > 60$  mm Hg and nocturnal oxyhemoglobin desaturation have an improvement in pulmonary hemodynamics that favorably affects exercise performance or survival have not been established to date.

#### Effect of Long-Term Oxygen Therapy on Exercise Performance

Patients with severe chronic air flow obstruction have limited exercise endurance primarily because of a reduced ventilatory reserve.<sup>35</sup> In both normal individuals and patients with severe chronic obstructive lung disease, supplemental oxygen improves exercise performance. This improvement has been thought to result from an increase in oxygen transport or a greater utilization of oxygen by exercising muscles,<sup>36,37</sup> and/or a delay in inspiratory muscle fatigue.<sup>38</sup> Moreover, an improvement in exercise endurance while inspiring supplemental oxygen has been attributed to an improvement in right ventricular function<sup>39</sup> and a decrease in ventilatory work load because of decreased airways resistance.<sup>40</sup>

Cotes and Gilson<sup>41</sup> was among the first to determine the effect of supplemental oxygen on improving exercise ability in patients suffering from chronic respiratory failure. In 22 of 29 patients, they found that breathing 30% oxygen significantly increased the time subjects could walk on a treadmill, compared with breathing room air oxygen. Leggett and Flenley<sup>42</sup> similarly found that patients suffering

from severe chronic bronchitis and resting hypoxemia showed increased exercise tolerance (as assessed by the distance they could walk on the level in 12 minutes) while inspiring oxygen. However, they found this improvement in exercise tolerance was negated when subjects were forced to carry their portable oxygen supply. The improvement in walking distance was restored when supplemental oxygen used during exercise was provided by wheeling the oxygen source on a lightweight trolley. Several other investigators confirmed the findings that patients who are hypoxemic at rest had a significant improvement in exercise tolerance when provided supplemental oxygen. Additionally, Davidson et al<sup>43</sup> showed a dose-dependent effect of supplemental oxygen on improving exercise performance, such that 17 patients with severe air flow obstruction when provided supplemental oxygen at a flow of 2 L/min increased their endurance for cycling time at a constant work load by 51%, compared with room air, by 88% at 4 L/min, and by 80% at 6 L/min.

Determining which patients suffering severe chronic obstructive lung disease may show improved exercise with supplemental oxygen has been more problematic. Cotes and Gilson<sup>41</sup> suggested that those patients who benefited most in improved exercise capacity from supplemental oxygen would have the largest venous admixture at rest, the greatest decrease in  $P_{aO_2}$ , and the greatest increase in  $P_{aCO_2}$  during exercise. Bradley et al<sup>44</sup> studied 26 patients with severe COPD who exercised on a treadmill while breathing room air or supplemental compressed air or oxygen. Although they found, as did others, that treadmill exercise endurance time was significantly increased while inspiring supplemental oxygen, no relationship was found between increased endurance and the degree of hypoxia, hypercarbia, or acidosis during exercise, or the change in these parameters while breathing oxygen, compared to breathing air.

Identifying the mechanisms responsible for the improvement in exercise endurance while inspiring supplemental oxygen in hypoxemic or normoxemic individuals has been similarly problematic. Although several investigators have found that inspiring supplemental oxygen during exercise reduces the perception of breathlessness, the mechanisms for this have remained a matter of debate. In fact, some investigators have attributed the reduction in perceived breathlessness to the effect of a cold stream of gas on nasal mucosal receptors rather than improved oxygenation. However, Swinburn et al<sup>45</sup> found in 12 patients with severe COPD with resting hypoxemia ( $P_{aO_2}$   $50 \pm 3.7$  mm Hg) that inspiring 28% oxygen, in contrast to compressed air, via air-entrainment mask, was associated with significant improvement in  $S_{aO_2}$  ( $85.1 \pm 2.3\%$  vs  $93.1 \pm 1.4\%$ ) and a reduction in breathlessness. Furthermore, when patients breathed oxygen, minute ventilation was significantly reduced compared to when they breathed air. The authors concluded that hypoxemic, breathless patients with ob-

structive lung disease benefited symptomatically from supplemental oxygen because of the effects of increased arterial oxygen associated with decreased minute ventilation due primarily to a reduction in tidal volume.

Besides the reduction in minute ventilation while inspiring oxygen, other investigators have attributed oxygen exercise improvement to increased peripheral oxygen delivery, improvement in pulmonary hemodynamics and right ventricular function, or to improved respiratory and non-respiratory skeletal muscle function. Morrison and Stovall<sup>46</sup> found that hypoxemic COPD patients who showed improved exercise capacity with supplemental oxygen had significant increase in oxygen delivery during exercise, which was associated with increases in both cardiac output and oxygen content, in contrast to those who had no improvement in exercise endurance. They attributed the increase in exercise capacity to a global increase in oxygen delivery rather than to a relief of hypoxic vasoconstriction. Similar data suggesting an effect of supplemental oxygen on improving exercise capacity on central hemodynamics and right ventricular function were demonstrated in the NOTT study.<sup>14</sup> In that study, breathing oxygen was associated with reduction in cardiac index, right ventricular stroke work index, and mean pulmonary artery pressure at rest. Furthermore, while performing the same magnitude of cycling exercise while breathing oxygen (in contrast to air), reductions in mean right atrial pressure, mean pulmonary artery wedge pressure, pulmonary vascular resistance, and stroke work index were found. Similarly, Dean et al<sup>47</sup> studied 12 patients with severe COPD in a randomized, double-blind, crossover protocol in which the patients exercised while they inhaled either compressed air or 40% oxygen. Dyspnea, cycle ergometry endurance time, and right ventricular systolic pressures (via doppler echocardiography) were measured during supine incremental exercise tests. The investigators found that the duration of exercise increased by 40% and the increase in dyspnea score was delayed while inspiring 40% oxygen. Furthermore, oxygen delayed the increase in right ventricular systolic pressure with incremental exercise and lowered the mean right ventricular systolic pressure at maximum exercise in all subjects. However, the increase in exercise duration only correlated with decrease in dyspnea, not with decrease in heart rate, minute ventilation, or right ventricular systolic pressure. Although the above studies demonstrate that oxygen may affect pulmonary hemodynamics, at rest and with exercise, the correlation of improvements in central pulmonary hemodynamics with increased exercise endurance is unclear at present.

Improvement in ventilatory muscle function has also been proposed as an additional mechanism of increased exercise endurance while inspiring supplemental oxygen. Bye et al<sup>38</sup> found in a group of severely obstructed patients that supplemental oxygen increased exercise performance,

Table 6. Indications for Long-Term Oxygen Therapy

|                                                                                                                           |                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Absolute                                                                                                                  | <ul style="list-style-type: none"> <li>• <math>P_{aO_2} \leq 55</math> mm Hg or <math>S_{aO_2} \leq 88\%</math></li> </ul>                                                                                                                       |
| In presence of cor pulmonale                                                                                              | <ul style="list-style-type: none"> <li>• <math>P_{aO_2}</math> 55–59 mm Hg or <math>S_{aO_2} \leq 89\%</math></li> <li>• EKG evidence of "P" pulmonale, hematocrit <math>&gt; 55\%</math>, congestive heart failure</li> </ul>                   |
| Only in specific situations                                                                                               | <ul style="list-style-type: none"> <li>• <math>P_{aO_2} \geq 60</math> mm Hg or <math>S_{aO_2} \geq 90\%</math></li> <li>• With lung disease and other clinical needs such as sleep with nocturnal desaturation not corrected by CPAP</li> </ul> |
| If the patient meets criteria at rest, $O_2$ should also be prescribed during sleep and exercise, appropriately titrated. |                                                                                                                                                                                                                                                  |
| If the patient is normoxemic at rest but desaturates during exercise or sleep                                             | <ul style="list-style-type: none"> <li>• (<math>P_{aO_2} \leq 55</math> mm Hg) <math>O_2</math> should be prescribed for these indications</li> <li>• Also consider nasal CPAP or bi-level positive airway pressure</li> </ul>                   |

$PaO_2$  = arterial oxygen tension.  $SaO_2$  = arterial oxygen saturation. EKG = electrocardiogram. CPAP = continuous positive airway pressure. (From Reference 51, with permission.)

which was accompanied by a reduction in minute ventilation and breathing frequency, in contrast to breathing air. In some of these subjects there was a delay in the appearance of the electromyographic pattern of diaphragm fatigue. Criner and Celli<sup>48</sup> found in a crossover, prospective trial that inspiring supplemental oxygen during exercise altered ventilatory muscle recruitment. They studied 6 patients who had severe COPD, mild hypoxemia at rest (mean  $P_{aO_2}$   $66 \pm 6.2$  mm Hg), and minimal arterial oxygen desaturation during exercise. They recorded pleural and gastric pressures while the patients inhaled either air or 30% oxygen during leg cycling. At rest, transdiaphragmatic pressure was lower ( $23 \pm 4$  cm  $H_2O$  vs  $26 \pm 7$  cm  $H_2O$ ,  $p < 0.05$ ) while inspiring 30% oxygen, compared with air, with an identical pattern of pleural and gastric pressure contraction while breathing either gas mixture. Similarly, measurements of maximum transdiaphragmatic pressure were no different while breathing either gas mixture. During exercise, transdiaphragmatic pressure increased similarly while breathing air with 30% oxygen, but while inspiring 30% oxygen there was a significant increase in peak inspiratory gastric pressure and decrease in peak inspiratory pleural pressure and expiratory gastric pressure, signifying a change in the pattern of respiratory muscle contraction during exercise. These data were interpreted as indicating that exercising with oxygen caused a redistribution of ventilatory muscle recruitment that enabled more dynamic work to be done by the diaphragm and less by the accessory inspiratory and abdominal expiratory muscles, thereby contributing to an increase in exercise time and a decrease in perceived work. Mechanisms for this improvement in diaphragm function, however, were not provided in this study.

Payen et al<sup>49</sup> reported that acute correction of hypoxemia in COPD patients results in a decrease of the ratio of inorganic phosphate to phosphocreatine (Pi/PCr), an increase in intracellular pH, and an increase in the resynthesis rate of creatinine phosphate during oxygen supplementa-

tion. The authors suggested these changes occurred secondary to an improvement in adenosine 5-triphosphate synthesis from oxidative phosphorylation and a reduction in anaerobic metabolism while breathing oxygen. Further data substantiating an improvement of LTOT on skeletal muscle metabolism were provided by Jakobsson and Jorfeldt.<sup>50</sup> They studied 8 patients with severe COPD, 4 of whom had chronic hypoxemia, and obtained quadriceps femoris muscle biopsies before and after 8 months of LTOT. Similar tests were performed in 8 healthy controls. In contrast to healthy controls, COPD patients had a 42% reduction in muscle glycogen, 21% reduction in adenosine 5-triphosphate and creatine phosphatase, 21% higher concentrations of creatine, and 90% higher concentrations of lactate. After using LTOT, the energy index (ratio of creatine phosphate [CrP] to CrP and creatine) increased 12% in the patients receiving LTOT but decreased 12% in the control COPD patients. The authors interpreted their results as showing that an improvement in skeletal muscle energy metabolism occurs during LTOT in patients with severe COPD and chronic hypoxemia.

Most studies suggest that patients who are hypoxemic at rest experience worsened oxygenation during exercise and that supplemental oxygen improves their exercise endurance. In addition, patients who are normoxemic at rest but experience exercise-induced desaturation also generally show improvement with supplemental oxygen. Although the exact mechanisms of the improvement in exercise endurance with supplemental oxygen are not definitely delineated at present, multiple factors appear to be involved, including improved cardiac function, reduced ventilatory work load, reduced pulmonary artery pressure, and improved respiratory and nonrespiratory skeletal muscle function.

### Summary

In general, based on the above studies of the effects of supplemental oxygen on reducing mortality and improving

sleep and exercise function in certain patient groups, patients whose disease is stable on a full medical regimen with  $P_{aO_2} \leq 55$  mm Hg ( $S_{aO_2} \leq 88\%$ ) should be considered for LTOT. Patients with  $P_{aO_2}$  of 55–59 mm Hg with signs of tissue hypoxemia (ie, cor pulmonale, polycythemia, impaired cognition) should also be considered for LTOT. Oxygen therapy should also be considered for those who desaturate during sleep or exercise. These guidelines have been adopted by Medicare as reimbursement criteria and have also been endorsed by the American Thoracic Society.<sup>51</sup> Indications for LTOT endorsed by the American Thoracic Society and published in the "Standards for the Diagnosis and Care of Patients with COPD"<sup>51</sup> are shown in Table 6. More research is required to investigate the use of supplemental oxygen in patients who suffer nocturnal desaturation but do not have signs of end organ dysfunction, those who have an improvement in dyspnea with supplemental oxygen, and in normoxemic patients with impaired exercise performance who improve while inspiring supplemental oxygen.

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## Discussion

**Zielinski:** I wanted to comment on the paper done by Sliwinski et al that you mentioned in your talk. You mentioned about the responders and non-responders to acute oxygen administration. We performed that study to challenge the results of studies performed by Ashutosh and Dunskey published in the blue journal<sup>1</sup> and *Chest*.<sup>2</sup> They found that responders lived longer than nonresponders. A strange thing in those studies was that the majority of patients, when given acutely oxygen, reacted with an important decrease in a pulmonary artery pressure, more than 5 mm Hg (responders). In our experience, if a patient is in a re-

ally stable state, free of exacerbation for several months, the reaction to acute oxygen is almost nil. A similar observation was made in the NOTT study. When the patients in the NOTT study were given acutely oxygen, the decrease in pulmonary artery pressure was negligible. So, we wanted to verify Ashutosh's opinion that responders live longer. We repeated Ashutosh's study and found that very few patients react to acute oxygen administration with an important decrease in pulmonary artery pressure. We followed our patients for 3 years and did not find a difference in survival between responders and nonresponders. My second comment concerns effects of nocturnal desaturations and of the

nocturnal oxygen treatment presented in a series of papers by Fletcher et al. His results are now challenged by the European group led by Dr Weitzenblum from Strasbourg. Perhaps tomorrow we will have more time to discuss this.

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# Effects of Long-Term Oxygen Therapy on Neuropsychiatric Function and Quality of Life

Jadwiga A Wedzicha MD

## Introduction

### Neuropsychological Function

#### Chronic Hypoxemia

#### Effect of Long-Term Oxygen Therapy on Neuropsychological Function

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#### General Quality of Life Questionnaires

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### Chronic Hypoxemia and Quality of Life

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#### Activities of Daily Living

## Conclusions

[Respir Care 2000;45(1):119–124] *Key words: long-term oxygen therapy, neuropsychiatric function, quality of life, chronic obstructive pulmonary disease, hypoxemia, dyspnea, activities of daily living.*

## Introduction

Patients with severe chronic obstructive pulmonary disease (COPD) complicated by chronic hypoxemia complain of disabling breathlessness and reduced exercise capacity. However the relationship between lung function, exercise capacity and dyspnea is not strong, suggesting that other factors are important in modulating health status in these patients. Patients with severe COPD suffer from cognitive impairment, anxiety and depression, which is more common than in a control population.<sup>1,2</sup> Thus many factors, not only social and physical, but also patients' expectations and their hopes and fears may contribute to impaired health status in patients with severe COPD.<sup>3</sup> Exercise dyspnea may increase anxiety and lead to loss of control over their disease.<sup>3</sup> Jones et al have shown that although 50% of the variance in a disease-specific quality of life questionnaire can be explained by cough, wheeze, walking distance, and anxiety, that still left 50% of the variance in the health score attributable to other factors.<sup>4</sup>

The reason for the psychological dysfunction in patients with chronic hypoxemia is largely unknown. It is unlikely that direct effects of hypoxia on brain metabolism are important, and some action on brain neurotransmitters, coupled with the effects of aging in this population, are more probable.<sup>5</sup> In this review I will first consider the effects of chronic hypoxemia on neuropsychological function in COPD patients and the effects of long-term oxygen therapy (LTOT). I will then consider aspects of quality of life and daily activities in severe COPD patients and any effects of LTOT.

## Neuropsychological Function

### Chronic Hypoxemia

There are two main approaches to the assessment of neuropsychological function. One is the battery approach, in which the Halstead-Reitan Neuropsychological Battery has been most extensively used.<sup>6</sup> The other method is the hypothesis-testing or Boston Process approach, focusing on the process of a patient's behavioral response. The first description of neuropsychological abnormalities was made by Krop et al, who studied a group of patients on LTOT and a control COPD group.<sup>7</sup> They found impairment in simple motor domains and visual spatial domains in the hypoxemic group. After one month of LTOT there was some improvement in neuropsychological function and

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memory. A study by Borak et al evaluated psychological status in patients on LTOT or about to start LTOT. There was no difference between these two groups in psychological scores, though anxiety, depression, and low self esteem were frequent findings in the study.<sup>8</sup>

Similar neuropsychological testing was performed in both the Nocturnal Oxygen Therapy Trial (NOTT) and the Intermittent Positive Pressure Breathing (IPPB) study, though the IPPB trial included patients with variable degrees of hypoxemia.<sup>9,10</sup> This allowed combinations of the data, and, of the 27 variables measured, 4 factors were determined: verbal intelligence, perceptual learning, problem-solving, and simple motor skills.<sup>11</sup> They found that COPD patients performed progressively worse with hypoxemia on all tests except verbal intelligence. Perceptual learning and problem-solving were found to be the most sensitive factors in differentiating between the groups with progressive hypoxemia.

### Effect of Long-Term Oxygen Therapy on Neuropsychological Function

The largest study of the effects of LTOT on neuropsychological function was in the NOTT study, wherein 150 patients were assessed over a 6-month period, with about 50% each in the continuous group (COT) and the nocturnal group (NOT).<sup>12</sup> A small sample of only 37 patients was examined after one year of LTOT therapy. Overall, there were improvements in function in both groups at the 6-month follow-up point. However at 12 months, the COT group performed better than the NOT group on the majority of the neuropsychological tests, though the number studied in the two groups was relatively small and the changes observed were subtle. Further analysis suggested that small improvements were observed in such functions as simple motor and verbal skills, flexibility of thought, and sensory abilities.<sup>12</sup>

### Measurement of Quality of Life

The fact that measurements of lung function are not directly related to exercise capacity and dyspnea has stimulated interest in the measurement of quality of life. Initially, general health questionnaires were used, but the need to evaluate interventions in COPD patients has also lead to the development of disease-specific measures of health status.

### General Quality of Life Questionnaires

A number of general questionnaires are available that have been widely used, including the Sickness Impact Profile (SIP), the Medical Outcome Study, and the Quality of Well-Being questionnaire.<sup>13-15</sup> General health measures were developed to provide an estimate of impaired health

due to a wide range of diseases, so the proportion of items relevant to any particular disease may be low. Early studies have shown a weak correlation between hypoxemia and quality of life, but used these general questionnaires rather than those specific for COPD.<sup>1,15,16</sup> Generally the SIP questionnaire has been shown not to be sensitive to change in studies of COPD interventions. A previous review of the SIP concluded that this instrument is relatively insensitive in COPD patients, as the scores remain in the mildly abnormal range until the forced expiratory volume in the first second (FEV<sub>1</sub>) falls below 50% of the predicted normal.<sup>17</sup> The Quality of Well-Being questionnaire has some advantages in that it has the properties of a utility scale, which can be useful in health economic studies. This questionnaire has been used in a major study of the effects of pulmonary rehabilitation, though there were no changes observed in scores after rehabilitation.<sup>18</sup>

### Disease-Specific Questionnaires

Disease-specific questionnaires were developed because of the potential insensitivity of the general measures. All of the items in such questionnaires are relevant to the condition under study. The Chronic Respiratory Questionnaire was the first of these that has been shown to be sensitive to change and reproducible.<sup>19</sup> It is divided into 4 dimensions: dyspnea, fatigue, mastery, and emotion, with response graded on a 7-point Likert scale. The dyspnea component is individualized and sensitive to change, especially after exercise training.<sup>20,21</sup>

The St George's Respiratory Questionnaire (SGRQ) is fully standardized, self-administered, and repeatable.<sup>3,4</sup> It has 76 items that are weighted to produce 3 component scores (symptoms, activities, and impacts), from which a total score is calculated. Scores vary from 0 (no disability) to 100 (maximum disability). The major difference between the SGRQ and the Chronic Respiratory Questionnaire is in the method of scoring. The SGRQ has been used to evaluate a number of interventions, and is sensitive to change.<sup>22,23</sup> All the items in the SGRQ were chosen because they were relevant to the daily lives and well-being of the patients, not because of a demonstrated relationship to a particular variable. Figure 1 shows the relationship between FEV<sub>1</sub> and quality of life using the SGRQ questionnaire, and shows that within a population the correlation between these two factors is weak.<sup>3</sup> Thus, in an individual patient, the FEV<sub>1</sub> does not accurately predict health status, and other measures are required.

### Chronic Hypoxemia and Quality of Life

Quality of life issues were addressed in the NOTT trial, with the SIP questionnaire administered.<sup>1</sup> Compared to a control group, hypoxemic patients had significant impair-

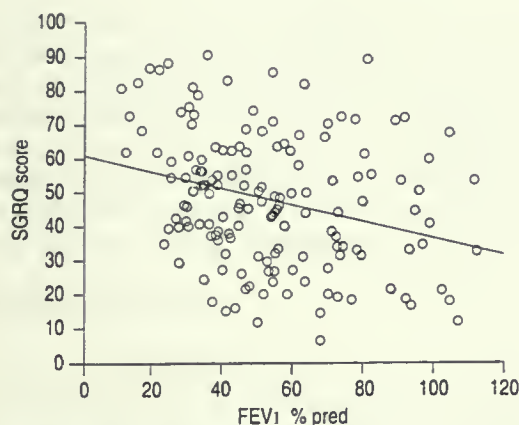


Fig. 1. Relationship between forced expiratory volume in the first second ( $FEV_1$ ) and health status, measured using the St George's Respiratory Questionnaire (SGRQ), from one study of COPD;  $r = 0.3$ ,  $p < 0.001$ . (From Reference 3, with permission.)

ment in most domains of the SIP questionnaire. A relationship was found between neuropsychological impairment and quality of life scores. However there was no relation between arterial oxygen tension ( $P_{aO_2}$ ) and quality of life scores.<sup>1,16</sup>

Okubadejo et al investigated the relationship between blood gases and quality of life, using both general and disease-specific questionnaires, in a group of 41 patients with severe COPD and mean  $P_{aO_2}$  of 56 mm Hg, studied on two occasions.<sup>24</sup> At the time of the study, patients who qualified for LTOT had not yet started therapy. In this study, as in previous ones, attempts to correlate hypoxemia with impaired health measured by a general questionnaire failed. However, there was a relationship observed between hypoxemia and SGRQ, in that  $P_{aO_2}$  was associated with higher and thus worsening quality of life scores (Fig. 2). As in previous studies, an association was also found between quality of life and anxiety and depression.<sup>1,16</sup> In this study, multivariate analysis showed that the effect of  $P_{aO_2}$  on quality of life was independent of the effect of mood state. The SGRQ symptoms and impacts were correlated with the levels of hypoxemia, but the activity score was not, and there was also no relationship between  $FEV_1$  and SGRQ. There was an association of marginal significance between the  $P_{aCO_2}$  and the SGRQ.

Seemungal et al recently reported a study relating COPD exacerbation to quality of life in patients with moderate to severe COPD.<sup>25</sup> They found that exacerbation frequency was related to SGRQ scores and that patients who were frequent exacerbators (three or more exacerbations per year) had significantly higher SGRQ scores, indicating worse health status than patients with less than three exacerbations per year. Thus some of the impairment of health status in chronic hypoxemia may be due to the effect of exacerbation, which becomes more frequent with increased

severity of disease. However, LTOT has not been shown to reduce COPD exacerbations, and this may account for the lack of effect of LTOT on quality of life scores, as discussed below.<sup>1,26</sup>

### Effect of Long-Term Oxygen Therapy on Quality of Life

Although impaired health status is common in LTOT patients, it may be argued that LTOT can further reduce quality of life, in view of the restricted mobility and noise disturbance suffered by these patients with the home equipment. In the NOTT study using the SIP questionnaire, a small but statistically significant improvement in quality of life, compared to the control group, was found after 6 months, when the COT and NOT patients were combined.<sup>9</sup> However, the clinical importance of these small changes was not clear and may have been due to the greater attention given to the LTOT patients. In a separate analysis of the NOT and COT groups, and compared to normal controls, the SIP was used to measure health status and Profile of Mood states to measure mood disturbance.<sup>12,27</sup> The authors reported no significant differences in the changes in the scores between the two groups over the study period. In one uncontrolled study, LTOT had no effect on general activity and independence, depression, or coping skills over 6 months.<sup>28</sup> Another uncontrolled study showed that 83% of patients using an oxygen concentrator for the provision of LTOT felt that their general well-being had improved because of the treatment.<sup>29</sup>

Okubadejo et al studied a group of patients who were assessed to start LTOT and another group of COPD patients with less severe hypoxemia.<sup>26</sup> A matched control group was not possible because it would have been unethical to withhold oxygen therapy from severely hypoxemic patients. All patients were followed for 6 months, with assessment of health status using SGRQ and SIP, and assessment of anxiety and depression using the Hospital Anxiety and Depression score.<sup>30</sup> Patients receiving LTOT had a slightly greater improvement in their quality of life than did the control group, but the difference was not statistically significant (Fig. 3). The lack of change may have been due to insensitivity, though this questionnaire has been used in other intervention studies with adequate response.<sup>22,23</sup> This study may also have had insufficient power for detection of a small change in quality of life. Neither quality of life scores nor their components were related to the level of hypercapnia,  $FEV_1$ , or age. Thus, LTOT does not have a major beneficial effect on quality of life, but it also does not reduce health status.

In this study the severely hypoxemic group initially had higher mean anxiety and depression scores than the control COPD group.<sup>26</sup> After 6 months the study group had become less anxious and the control group more anxious,

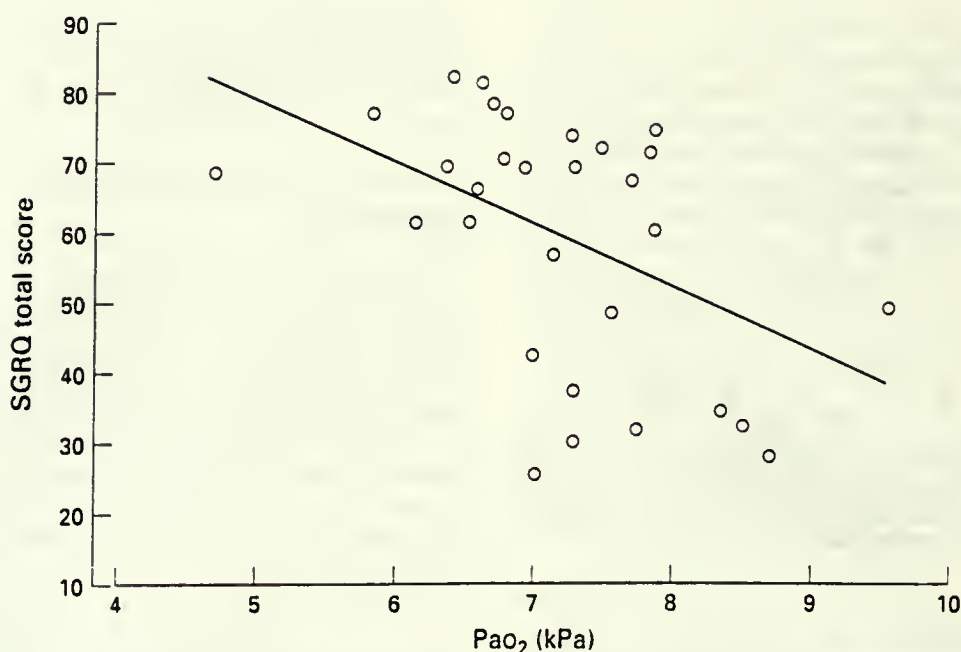


Fig. 2. Relationship between quality of life (St George's Respiratory Questionnaire [SGRQ] Total score) and degree of hypoxemia in patients with severe COPD ( $n = 41$ ,  $p < 0.01$ ).  $P_{aO_2}$  = arterial oxygen tension. (From Reference 24, with permission.)

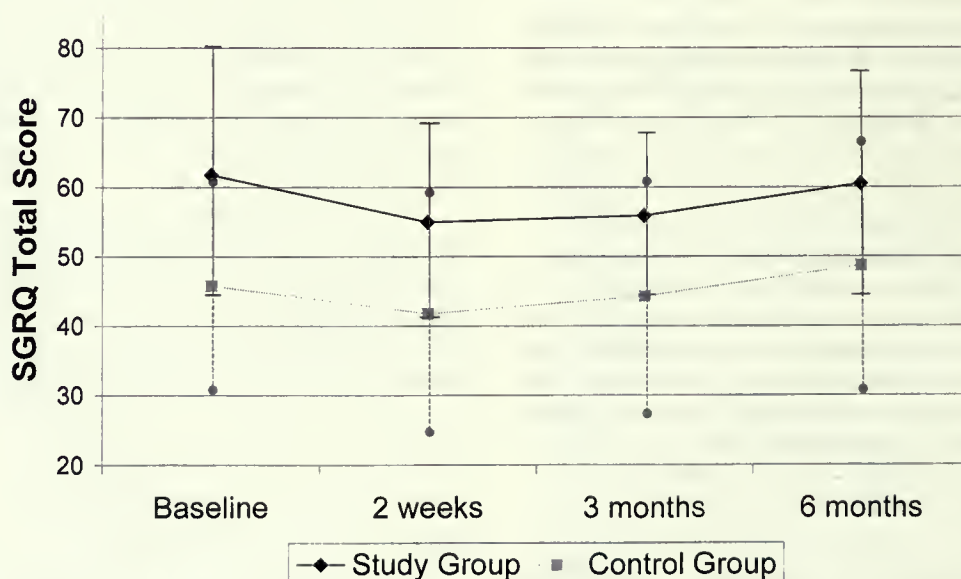


Fig. 3. Effects of long-term oxygen therapy on quality of life (St George's Respiratory Questionnaire [SGRQ] Total score) in hypoxemic patients ( $n = 19$ ) and in matched control COPD patients ( $n = 17$ ).

the difference being statistically significant. However, these changes were small and the suggestion that LTOT may have a beneficial effect on anxiety levels should be treated with caution. Depression scores after 6 months were higher both in the study and control groups and there was no difference between the groups.

One other issue is whether the oxygen delivery device affects quality of life. In a crossover study comparing

liquid and gaseous oxygen for ambulatory use, Lock et al found that patients used the liquid oxygen device for a longer period than the gaseous oxygen cylinder, and 11 out of 15 patients said they preferred the liquid device. However, there were no differences observed between the two study groups in any of the four domains of the Chronic Respiratory Questionnaire.<sup>31</sup> A recent study mainly concerned with a cost utility analysis of domiciliary oxygen

therapy compared patients receiving liquid oxygen to those using oxygen concentrators. The SIP scores showed that quality of life in patients on liquid oxygen was better than with concentrators, even though liquid oxygen was more expensive.<sup>32</sup> However, no disease-specific quality of life measure was used in this study. Further work is required to assess the effects of the delivery device on health status, in both sedentary and ambulatory patients.

### Activities of Daily Living

Patients with COPD experience disabling breathlessness that reduces exercise capacity and thus restricts activities of daily living (ADL). Although the goal of pulmonary rehabilitation programs has been to increase independence and increase ADL, few studies have specifically investigated the effect of COPD or hypoxemia on ADL. Furthermore, it has been suggested that the use of LTOT with a stationary source of oxygen can adversely affect independence and restrict activities in the home. A review of patients in the East End of London, United Kingdom (UK), showed that approximately 50% of patients with home oxygen concentrators are housebound.<sup>33</sup>

Traditionally, ADL measures have been used in patients with stroke and other disabling conditions of the elderly. ADL scales measure disability, and sometimes handicap, and are generally used to give some indication of an individual's ability to function independently in daily life. Using one ADL scale (the Nottingham Extended Activities of Daily Living Scale),<sup>34</sup> Garnham et al showed that ADL scores in COPD patients are related to exercise capacity.<sup>35</sup>

Okubadejo et al conducted a study in the patients' homes on a group of patients receiving domiciliary LTOT and a control group with severe COPD but without hypoxemia and thus not on LTOT.<sup>36</sup> They found similar scores between the groups in health status using the SGRQ, though the ADL scores were lower in the LTOT group (Table 1).

Table 1. Comparison of Health Status

|                       | LTOT        | Non-LTOT    | p value |
|-----------------------|-------------|-------------|---------|
| SGRQ total*           | 62.7 (17.6) | 55.4 (18.6) | 0.21    |
| SGRQ symptoms*        | 66.9 (19.5) | 69.5 (22.0) | 0.69    |
| SGRQ activity*        | 63.1 (21.0) | 59.2 (23.3) | 0.57    |
| SGRQ impacts*         | 62.1 (21.5) | 52.1 (23.9) | 0.17    |
| ADL score†            | 10 (2–20)   | 17 (6–22)   | 0.01‡   |
| HAD anxiety score†    | 6 (0–20)    | 6 (0–15)    | 0.98    |
| HAD depression score† | 7 (1–15)    | 6 (1–13)    | 0.21    |

SGRQ = St George's Respiratory Questionnaire. ADL = activities of daily living. HAD = hospital anxiety and depression.

\*mean (standard deviation)

†median (range)

‡p < 0.05

(From Reference 36, with permission.)

However, further analysis showed that the difference in the ADL scores was related to the level of FEV<sub>1</sub>, depression, and health status. This suggests that the reduced independence in ADL is not simply a result of the restriction of movement imposed by the stationary device. This study also found that although the ADL scores were lower in the LTOT group, they had similar SGRQ activity scores. Although this result may be due to relatively few questions in the SGRQ pertaining to patients being housebound, it may be due to reduced expectation of physical capacity as the disease progresses. Depression was related to loss of independence in ADL, and this emphasizes the complex interplay between dyspnea, exercise limitation, anxiety and depression, muscle wasting, quality of life, and disability.<sup>17</sup>

### Conclusions

Patients with chronic hypoxemia have frequent neuropsychological impairment that may contribute to the associated disability. Health status is also reduced in patients with COPD and chronic hypoxemia, and the SGRQ score is related to the P<sub>aO<sub>2</sub></sub>, with worsening health status with increased arterial hypoxemia. However, LTOT has little effect on health status, though it may reduce the progression of anxiety in hypoxemic patients. There is no evidence that health status is reduced with LTOT treatment. The reduced independence of these LTOT patients is not due to the effects of the LTOT equipment, but is related to the degree of air flow obstruction, depression, and poor health status.

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## Discussion

**Johnson:**\* Did you find there were any differences in patients if you administered anti-anxiety agents?

**Wedzicha:** Yes, there are relatively few studies in the literature looking at anti-depressants or anti-anxiety agents in this group of patients. I have used them, occasionally, with good effect. I must say I always think cognitive therapy would be very valuable to some of these patients. I didn't really discuss the NOTT neuropsychology data in a lot of detail, but a significant number of patients had clinical depression. In our data we found that fewer

of our patients actually had clinical depression, and most of the depression and anxiety was subclinical. I would have thought cognitive therapies are probably the way forward in these patients.

**Zielinski:** I've got a question concerning Paul Jones's study on salmeterol.<sup>1</sup> They found that the improvement in the St George's Questionnaire's score, by more than 4

\*Robert Johnson MD, Salter Labs, Arvin, California.

points, is significant. How did they come to this conclusion? In a 100-point scale, 4 points difference seems to be rather small.

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**Wedzicha:** The way they came to this conclusion was to look first of all at the variability of the questionnaire. But also they looked into early intervention studies and validated the change against improvements and symptoms and other factors, such as exercise and capacity. Tomorrow, I'm going to talk a little more about the use of this questionnaire, looking at patients who have been given nasal ventilation in addition to LTOT, where you will see that the changes are very much bigger than that.

**Pierson:** We talked earlier in our discussions about the barriers psychologically to patients in accepting oxygen therapy. You mentioned an anti-oxygen lobby in your remarks. In the UK are there components of the health care system that are against oxygen therapy?

**Wedzicha:** Certainly, we come up against patients, as I said earlier, who do not want to go on oxygen therapy. There is some reluctance among some physicians to use oxygen therapy. Some of it is related to using oxygen therapy in smokers, where there has been considerable discussion.

**Pierson:** We mentioned the late David Flenley earlier, and I remember hearing him say that patients who continue to smoke should not have oxygen. Are there still instances in the UK of oxygen being denied or removed from the homes of patients because they're found to be smoking?

**Wedzicha:** It is denied. We had extensive discussions at the Royal Col-

lege of Physicians prior to the UK guidelines being written, and I must admit that I was probably the strongest proponent that we should not discriminate against smokers, because the data really are not there to deny patients oxygen therapy. We have some data that smoking affects their exercise capacity, but generally the evidence that smokers do badly in the long term is not really available from trials. But I would still say that in the UK, probably about 50% of chest physicians would not want to prescribe oxygen to smokers. Again, I think there's an issue whether you use oxygen concentrators, which are low-flow oxygen, or pressurized systems for ambulatory care. There is more danger with the pressurized system than there is, probably, with the oxygen concentrators. Would you agree with that?

**Pierson:** Yes. Well, I don't know about that last statement, but I was going to say that, if the literature on smoking cessation teaches us anything, it is that patients don't tell the truth as to whether they're smoking or not. So that raises the issue of how you determine whether your patient is smoking or not.

**Wedzicha:** Absolutely. It is difficult to do cotinine levels on all our patients. This was the argument I myself kept putting forward. We all know that patients stop smoking for 2 to 3 days prior to coming to see physicians, but I think the long-term benefits of oxygen therapy outweigh, probably, the effects of some continual smoking.

**Benditt:** Fascinating data that you presented. With your long-term oxygen therapy versus control group, if I'm remembering correctly, they were more homebound and the depression scores were worse, but the quality of life showed no difference. What do you think quality of life is measuring in those people?

**Wedzicha:** There was no difference in quality of life in the group, and the only parameter was the change in the ADL. Depression was similar in the 2 groups. So I think the way we interpret it was that the patients, although they do less, they also *expect* to do less.

**MacIntyre:** I just want to make sure I understand something. When you analyzed the NOTT trial, did I understand you to say that the 2 groups on oxygen were better than at baseline?

**Wedzicha:** You mean our own data, or the NOTT data?

**MacIntyre:** The NOTT data you showed up there. It was interesting that they had poor scores, poor neuropsychiatric function, and then after 6 months, when the scores were repeated, not much happened. Then after 12 months, they were different. So the long term was better than the nocturnal?

**Wedzicha:** Yes.

**MacIntyre:** Another question, and this also applies to Jerry Criner's data on hospitalization in the NOTT trial. The people on nocturnal oxygen were dying more than the people on the continuous oxygen. Would the people who would've been using hospitalizations and been more depressed, be, therefore, dropping out? Were these comparisons taking into account the fact that the mortality was higher and more people were dying in the nocturnal group?

**Wedzicha:** I'm sure Tom Petty could fill us in, because I presume he has seen these data many times. The point about the 12-month data is that there were only about 17 patients left in each group. Tom, is that correct, that by the time they were assessed at 12 months, the numbers were so small?

**Petty:** Well, that's partly right. But one of the things about the NOTT study is that all the patients didn't enter at the same time, so they were all in the queue going down the line,

and that's when we had the data monitoring board because no individual center knew what the statistical outcome was going to be. For example, in Denver, we had 28 patients, and

in Winnipeg I think there were 40. So you couldn't discern whether NOT was worse than COT in any individual center. But the data monitoring board could.



**Lung Sounds: A Practical Guide**, 2nd edition. Robert L Wilkins MA RRT, John E Hodgkin MD, and Brad Lopez MS RRT. St Louis: Mosby, 1996. Softcover, illustrated, 114 pages plus audiocassette (50 min), \$43.

All competent respiratory therapists agree that excellent assessment skills are fundamental to sound clinical practice. Despite the recent emergence of a debate concerning its importance, the stethoscope has remained one of the most basic tools of assessment. This is good news for the authors of **Lung Sounds: A Practical Guide**, who are committed to the belief that the stethoscope is an essential tool, one that's here to stay. Their multimedia package (audiotape and 114-page paperbound book) provides detailed information aimed at helping respiratory care, nursing, or medical students understand those mysterious sounds that emit from patients' chests.

The book is a well written guide to general chest assessment. At just over 100 pages, the text is focused and succinct, yet thorough. Its 5 chapters provide both very general and highly specific information. The first chapter presents a complete if perfunctory overview of respiratory anatomy and physiology. It is well diagrammed, with thoughtfully selected and clinically relevant figures. Though the narrative is comprehensive, a background in general anatomy and physiology is desirable. Chapter 2 covers general chest assessment completely and clearly. But, like respiratory anatomy and physiology, it covers a topic so broad that discussion is necessarily limited in some areas. Overall, however, basic examination techniques and findings are well covered.

The third chapter discusses in extensive detail each of the many specific sounds heard over airways. The next chapter reminds the reader of pulmonary teaching rounds, as it focuses on clinical application. This approach extends to the final chapter, in which the authors present 7 interesting case studies for analysis by the reader. Chest radiographs, past and present medical history, and physical exam information accompany each case study. Critical thinking questions help the reader to puzzle through each case.

The book's two appendixes include a list of sounds presented on the accompanying audiotape, and a post-test that can be used for continuing education credits (thus, no key is provided). The volume is well indexed.

At 25 minutes, the audiotape presents every lung sound described in Chapter 4, as well as the sounds accompanying the case studies of Chapter 5. Each example is sufficient in length to provide the listener with a solid idea of what he or she is hearing. Sound reproduction is excellent: clarity is good whether the listener listens with a stethoscope over the tape player's speaker, or through personal stereo headphones.

The tape provides no narrative, explanation, or discussion. Rather, an announcer simply reads the names of the specific breath sounds being demonstrated, or identifies which sounds accompany each case study. I found this sparseness of commentary mildly surprising but not problematic.

However, I was frankly more surprised when I turned the tape over and found the opposite side blank. As recorded, the tape is sufficient for the authors' purpose, but I feel they may have missed an opportunity for further teaching. A clinically oriented discussion might have enhanced the learner's appreciation of the finer points of lung sounds. Perhaps the second side could have focused on the book's case studies, pointing out essential features of each case and explaining how the breath sounds presented were relevant. Or it could have included a discussion of the fine points of distinguishing breath sounds, as a means of reinforcing the text. If these suggestions do not suit the authors' purpose, then a final suggestion for future printings is to rerecord the audiotape to minimize the annoyance of lengthy rewinding. This could be accomplished by simply duplicating the same sounds on both sides, or by splitting the information equally between the two sides.

The lack of these features on the tape, though, does not diminish the quality of the information presented. The authors have developed a well researched and well designed learning package that will meet most learners' needs. It most certainly should be a part of every school's library, and would make a

fine addition to every respiratory therapist's collection.

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**Physiotherapy for Respiratory and Cardiac Problems**, 2nd edition. Jennifer A Pryor MBA MSc and Barbara A Webber FCSP DSc, editors. Edinburgh, United Kingdom: Churchill Livingstone, 1998. Softcover, illustrated, 524 pages, \$39.95.

This second edition offers an overview of impairments and physiotherapy treatment approaches for individuals who have respiratory or cardiac dysfunction. The text, written by internationally known clinicians, provides a broad overview of the subject matter, but is written in a genre of care and approach that may seem outdated or not in synchrony with present day health care terminology and delivery in the United States.

The text includes new or revised information on surgery, intensive care, noninvasive ventilation, and pulmonary rehabilitation. The organization of the text is traditional—assessment techniques, imaging, cardiopulmonary function testing, noninvasive ventilation, followed by physiotherapy techniques and specific patient diagnostic categories or impairments. This text generally does not maximize the integration of the information in "support chapters" to the discussion of diagnosis/impairment and intervention chapters. A few chapters, including the chapters on spinal injuries and pediatrics, do provide nice integration of patient impairment, medical support, and intervention, which greatly increases the usability and applicability of these chapters.

It is striking to note the repeated advocacy or mention of use of intermittent positive-pressure breathing for patient populations such as following lobectomy or trauma, which does not match the scientific literature. The advocacy for use with patients who have true respiratory muscle weakness, fatigue, or paralysis is appropriately mentioned.

The manual techniques of physiotherapy are defined but not delineated or discussed

adequately under such chapters as "Intensive Care for the Critically Ill Adult." As well, the literature regarding use of these techniques for various impairments is richer than this text references.

Edited and contributed to by well known physiotherapists in the area of cardiopulmonary care, the text is clearly printed and the illustrations well done. The overall approach and discussions of treatment are often not consistent with present day research and health care delivery in the United States.

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**Thurlbeck's Chronic Airflow Obstruction**, 2nd edition. William Michael Thurlbeck MD and Joanne Lynne Wright MD. Hamilton, Ontario, Canada: BC Decker, 1999. Hardcover book (plus CD-ROM), illustrated, 332 pages, \$69.95.

Chronic air flow obstruction encompasses a variety of disorders, including chronic bronchitis, emphysema, asthma, and bronchiectasis. These disorders are very prevalent and have somewhat similar clinical presentations. Commonly, patients may have a combination of these diseases leading to their airway obstruction. Pathologically these disorders are very different, as are their purported etiologies.

**Chronic Airflow Obstruction** is intended to provide a clinicopathologic guide to the various disorders that cause air flow limitation. It is very well written, easy to read, and appropriately divided into 10 chapters. The book begins with a historical review of research in the field of chronic airways disease that occurred up until the mid 20th century; it is a brief but interesting chapter. This is followed by a very good, concise review of pulmonary function testing and the patterns seen in the various disorders of the airways. The remaining chapters focus on the most common diseases that lead to chronic airflow obstruction.

The discussions of these disorders are heavily weighted to the pathologic abnormalities seen. For example, there is an extensive discussion of mucous gland enlargement and the Reid Index in the chapter on chronic bronchitis. There are very good reviews on the pathogenesis of these disorders, with discussions of basic science and animal model research. The reviews are cur-

rent, with references from as recent as 1998. This section is then followed by one on the epidemiology of the disease, which, particularly in the case of emphysema, is excellent. The strength of this book lies in the correlations and associations made between the pathologic findings and the clinical findings in the various diseases. For example in the chapter on emphysema, correlations are made between the pathologic severity of emphysema and pulmonary function testing and radiologic changes. This is also evident in the chapter on asthma; there are excellent tables comparing and contrasting the clinical and pathologic features in the different diseases that lead to airway obstruction. Finally, the last chapter discusses the effects of these airway disorders on other organ systems, such as the liver and kidneys. This a unique and very interesting chapter.

The text is clearly written, with no typographical, spelling, or grammatical errors. There are numerous tables, illustrations, and photographs, a very important feature for a book that has such a large clinicopathologic component. The index is well organized with major and minor headings. The bibliography for each chapter is extensive and very current. The book is a hardcover, neatly bound, and accompanied by a CD-ROM that contains the entire text and illustrations in searchable PDF (portable document format) files.

I have few criticisms of the book. Criticisms include extensive discussions on the pathological findings in certain chapters. Somewhat necessary, but for the audience to whom this book is directed, the discussion on the technique of lung preparation for pathological examination in Chapter 5 is too detailed and prolonged. There are no discussions on the therapies of the disorders, which would be appropriate considering the aims of this book.

Without question this book, written by pulmonary pathologists, is heavily weighted on pathology. This is not an all-encompassing textbook on diseases that cause chronic airflow obstruction. Rather it is an excellent text that reviews the pathology, pathogenesis, and clinical presentation of diseases that cause chronic airflow obstruction. The target audience will be predominantly pulmonary physicians, allergists, and pulmonary pathologists, but also general internists, family practitioners, pediatricians, pulmonary nurses, and respiratory therapists who are

interested in reading in more detail on these disorders.

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**Peer Review in Health Sciences**. Fiona Godlee and Tom Jefferson, editors. London, United Kingdom: BMJ, Books, 1999. Soft-cover, illustrated, 271 pages, £30 (\$48).

I began **Peer Review in Health Sciences** in a straight-backed chair at my desk, assuming that reading it to produce a book review would be work. I soon moved to an easy chair, having found the book to be interesting, informative, entertaining, and readable.

**Peer Review in Health Sciences** covers peer review at two ends of the research spectrum: grant applications and manuscripts submitted to journals. The book describes what peer review is, how it developed, its effectiveness, and its defects (such as bias and misconduct). The book also provides practical guides on how to peer review grant applications and manuscripts, with specific advice for reviewing statistics and economics. Finally, it suggests ways to improve the current review system, particularly by using the Internet.

The book's editors are Fiona Godlee, an editor with the *British Medical Journal*, and Thomas Jefferson, a researcher with the Cochrane Centre (for systematic reviews) in Oxford. The authors of individual chapters are evenly divided among journal editors, statisticians, and researchers. Many display an insider's knowledge: "... we decided to investigate..."; "I was a member of the commission..."; "we recently rethought our approach and developed a new streamlined system." One-quarter of the references in the chapter on "Statistical Peer Review" by Altman and Schulz are to their own work.

The intended readership comprises editors of medical journals and reviewers of submitted manuscripts and grant applications. Indeed, editors will find interesting attempts at justifying peer review based on ethics or economics and new ideas such as forward links to subsequent publications. Those new to reviewing will learn from "How To Peer Review a Manuscript," with advice that is particularly practical—such as declining to review if you do not have

time or familiarity with the subject—and specific, with citations of scoring systems.

In addition, novice authors will be interested in the chapter on “An Author’s Guide to Editorial Peer Review,” and all authors will want to read “Bias, Subjectivity, Chance, and Conflict of Interest in Editorial Decisions.” Researchers will be interested in “Peer Review of Grant Applications: A Systematic Review” and “Bias in Peer Review of Research Proposals.”

Judging by those chapters about which I have some knowledge, the content seems thorough, well evidenced, and accurate. “The state of evidence: what we know and what we don’t know about journal peer review” and “Bias, Subjectivity, Chance, and Conflict of Interest in Editorial Decisions” are especially comprehensive.

The writing is clear, logical, and well organized. Although most is pedestrian, some writing is extremely colorful: “. . . if scholarly publication is not to degenerate into some vast and chaotic chat page . . .”; “. . . one can seldom contemplate repeating a [clinical] trial should things go wrong . . . recruiting another group of patients is not the same as ordering another batch of rats”; “The time between a journal accepting a paper and actually publishing it is called the lead time (lead as in dog lead, rather than lead the heavy element)”; “The only limitation to publication [is] a lack of stamps.” However, a few analogies (eg, “funding at the National Institutes of Health follows a biblical pattern” and “ring-fenced funding”) should be explained.

Amusing anecdotes unfold: Yale Medical School stopped studying infectious disease, anticipating that antibiotics would cleanse the earth of pathogens, and a Swedish board withdrew funding from the development of ultrasound and echocardiogra-

phy because it saw no practical biomedical application. The chapter on “Misconduct and Journal Peer Review” reads like a who-done-it; the chapter on “Bias in peer review of research proposals” evokes outrage.

The authors proffer new ideas: having a journal ombudsman; justifying peer review on the basis of ethics; peer-reviewing editorials; posting e-prints (drafts) on a web site for comment before submitting a manuscript to a print journal.

While the chapter on “Peer Review of Grant Applications: a Systematic Review” refers to the chapter on “Bias in Peer Review of Research Proposals,” and “The Future of Peer Review” refers to “Peer Review on the Internet: Are There Faster, Fairer, More Effective Methods of Peer Review?” most chapters overlap without comment. This can be justified if most readers ingest only a few chapters, rather than the entire book.

The paperback cover detracts from the book’s appearance, but reduces purchase and mailing costs. The BMJ Bookshop (at <http://www.bmjbookshop.com>; accessed August 11, 1999) lists the price as £30.00 plus 30% for post and packing outside Europe. (The BMJ Bookshop lists the author as Tom Jefferson only, curious in light of the book’s comments on gender bias.) My university’s book store estimated a total cost of \$60 through its distributor. The typography is clear. The few illustrations, being line art, reproduce well. Inexplicably, cartoons are reproduced without attribution.

I noticed no typographical mistakes or errors in references. (This is to be expected, given the number of editors contributing.) Unfortunately, the indexer was not so thorough, relying heavily on headings. Starting with a topic in the text and checking to see whether it was indexed, I realized that one

beginning a search with the index would miss the common law definition of fraud on Page 90, the suggestion of CONSORT on Page 151, and the issue of blinding on Page 199. Looking under “Internet,” the searcher would miss the section on electronic review on Page 7; looking under “bias,” the searcher would miss the section about gender bias on Pages 64–67. (Although the index term electronic publication refers to Internet and there is a separate listing for gender bias.)

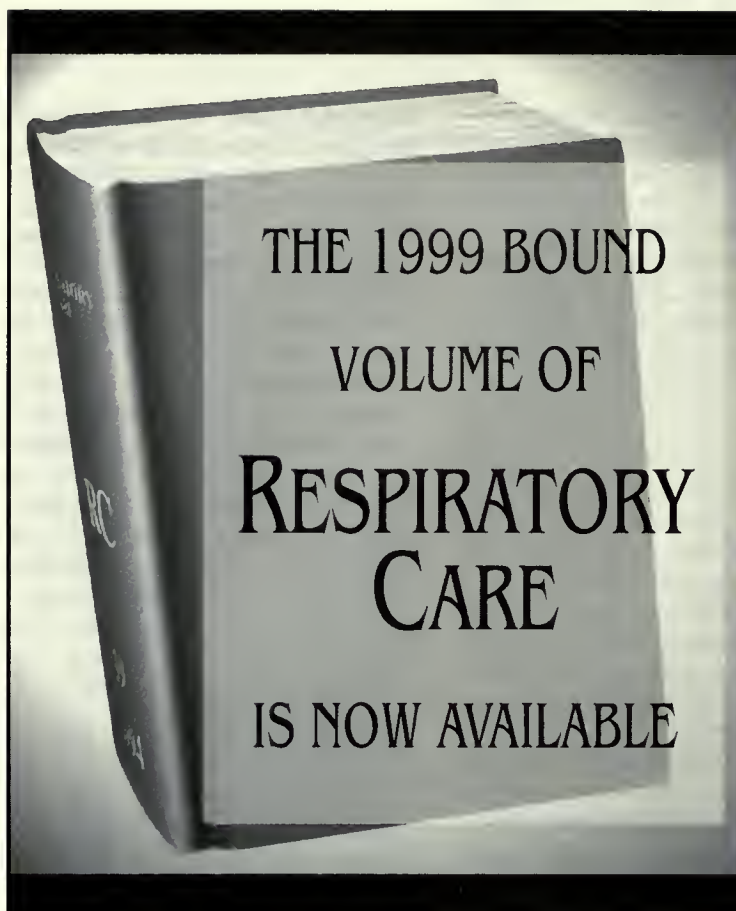
The book achieves its aims, providing a comprehensive reference and new ideas for those engaged in peer review. The big question is whether this book is of interest to a wider audience of clinicians, specifically, the therapists, technicians, nurses, and physicians reading *RESPIRATORY CARE*. The book’s introduction and the chapter on “The effectiveness of editorial peer review” give some insight.

What clinicians read affects how they treat their patients. Clinicians accept that editors and reviewers have selected what is offered for them to read. Clinicians also assume that being published in a reputable journal gives some assurance of an article’s quality. They may be surprised to find that the selection is biased and that quality is not guaranteed.

When clinicians are ready to look beyond the week-to-week and month-to-month content of medical journals to the big picture, they should order a copy of this book, find a comfortable place to sit, and enjoy reading *Peer Review in Health Sciences*.

**Carin M Olson MD**

Department of Medicine  
Division of Emergency Medicine  
University of Washington Medical Center  
Seattle, Washington



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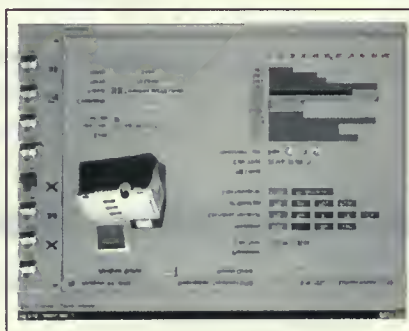


**Oxygen Sensor.** Servomex Transducers announces the worldwide launch of a brand new transducer based on a patented development of the paramagnetic oxygen measurement principle. According to the company, the Paracube® is small, low maintenance, and reliable. Servomex press materials also state that this device provides digital output, simple gas handling needs, and consistent performance. For more information from Servomex Transducers, circle number 173 on the product information card in this issue, or send your request electronically via "Advertisers Online" at [http://www.aarc.org/buyers\\_guide/](http://www.aarc.org/buyers_guide/)



**Nasal Gel Mask.** Respironics introduces the Profile™ Lite Nasal Gel Mask. The company says this new product has been

designed with a softer, lighter gel cushion and offers comfort and two-in-one convenience for patients using CPAP or bi-level positive airway pressure devices. According to Respironics, the Profile Lite weighs about 20% less than the mask's first design released early in 1999, and this new design is available in three sizes that will fit most patients. Additional sizes are available by special order, and standard sizes can be customized if necessary. For more information from Respironics, circle number 174 on the product information card in this issue, or send your request electronically via "Advertisers Online" at [http://www.aarc.org/buyers\\_guide/](http://www.aarc.org/buyers_guide/)



**Blood Gas Instrument Monitoring Software.** AVL Scientific Corporation has introduced its OMNI-Link™ remote control and diagnostic monitoring software for blood gas instruments. According to AVL, OMNI-Link allows professionals in laboratories, respiratory therapy departments, point-of-care testing venues, and administration to monitor instrument status, initiate instrument functions, and perform trouble-shooting routines—all from a remote location. Company press materials say that the new software features flexible connectivity options including TCP/IP ethernet, radio frequency networks, and standard serial RS-232 connections. They also say that

OMNI-Link is easy to operate and features large, easy-to-read graphics and on-board instructions. For more information from AVL Scientific Corporation, circle number 175 on the product information card in this issue, or send your request electronically via "Advertisers Online" at [http://www.aarc.org/buyers\\_guide/](http://www.aarc.org/buyers_guide/)



**Inhaler Adapter.** Boehringer Ingelheim announces its new inhaler adapter for elderly and arthritic COPD patients. Company press materials say this new device will help those patients who had been previously dependent upon nebulizers to receive their medications because they were unable to effectively use metered-dose inhalers. Boehringer Ingelheim says this adapter is designed for use with two leading treatments for COPD—Combivent® inhalation aerosol and Atrovent® inhalation aerosol—providing an easy-to-use hand pump to dispense the medication rather than having to depress the canister. For more information from Boehringer Ingelheim, circle number 176 on the product information card in this issue, or send your request electronically via "Advertisers Online" at [http://www.aarc.org/buyers\\_guide/](http://www.aarc.org/buyers_guide/)

## Scheduled Professor's Rounds 2000

**Pulmonary Rehabilitation: What You Need to Know**—Julien M Roy BA RRT; Host, Richard Branson BA RRT—Video March 7; Audio April 4

**Pediatric Asthma in the ER**—Tim Myers BS RRT; Host, Richard Branson BA RRT—Video March 28; Audio April 18

**Drugs, Medications and Delivery Devices of Importance in Respiratory Care**—Jim Fink MS RRT; Host, David Pierson MD—Video April 25; Audio May 16

**Cost Effective Respiratory Care: You've Got to Change**—Kevin Shrake MA RRT FACHE; Host, Sam P Giordano MBA RRT—Video 23; Audio June 20

**Pediatric Ventilation: Kids Are Different**—Mark Heulitt MD; Host, Richard Branson BA RRT—Video 25; Audio August 15

**What Matters in Respiratory Monitoring: What Goes and What Stays**—Dean Hess PhD RRT FAARC; Host, Richard Branson BA RRT—Video August 22; Audio September 26

**Managing Asthma: An Update**—Patti Joyner RRT CCM; Host, Mari Jones MSN RN RRT—Video September 19; Audio October 17

**Routine Pulmonary Function Testing: Doing it Right**—Carl D Mottram RRT RPFT; Host, David Pierson MD—Video November 7; Audio December 5



## Helpful Web Sites

### American Association for Respiratory Care

<http://www.aarc.org>

— Current job listings

— American Respiratory Care Foundation fellowships, grants, & awards

— Clinical Practice Guidelines

### National Board for Respiratory Care

<http://www.nbrc.org>

### RESPIRATORY CARE online

<http://www.rcjournal.com>

— 1998 Subject and Author Indexes

— Contact the editorial staff

### Asthma Management Model System

<http://www.nhlbi.nih.gov>

### Keys to Professional Excellence

<http://www.aarc.org/keys/>

## The National Board for Respiratory Care—2000 Examination Dates and Fees

| Examination            | Applications Accepted/<br>Testing Available | Examination Fees                                                           |
|------------------------|---------------------------------------------|----------------------------------------------------------------------------|
| CRT                    | Dec 1, 1999<br>Jan 10, 2000                 | \$190 (new applicant)<br>\$150 (reapplicant)                               |
| Perinatal/Pediatric    | Dec 1, 1999<br>Jan 10, 2000                 | \$250 (new applicant)<br>\$220 (reapplicant)                               |
| CPFT                   | Jan 1, 2000<br>Feb 1, 2000                  | \$200 (new applicant)<br>\$170 (reapplicant)                               |
| RPFT                   | Jan 1, 2000<br>Feb 1, 2000                  | \$250 (new applicant)<br>\$170 (reapplicant)                               |
| RRT<br>(Written & CSE) | Feb 1, 2000<br>Apr 1, 2000                  | \$190 (new - written only)<br>\$200 (new - CSE only)<br>\$390 (new - both) |

For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156, or e-mail: [nbrc-info@nbrc.org](mailto:nbrc-info@nbrc.org)

## AARC & AFFILIATES

### February 9-11, 2000—Portland, Oregon

The Oregon Society for Respiratory Care will host its annual Pacific Northwest Conference at the Monarch Hotel and Conference Center in Clackamas, OR.

"Respiratory Care in the New Millennium" will offer 17 hours of continuing education credit and will feature noted speakers Dr. Neil MacIntyre and Dr. Forrest Bird.

**Contact:** For information, call Tim Hutchison (503) 215-2628.

### February 9-11—David, West Virginia

The West Virginia Society for Respiratory Care will hold its Annual Winter Meeting at The Canaan Valley Resort. This unique conference allows participants the opportunity to acquire as many as 11 CECs while affording them the chance for cross-country or alpine skiing, hiking, ice skating, or simply relaxing by the indoor pool and Jacuzzi. Exhibits by many respiratory care equipment manufacturers and service providers will also be featured. Lecturers include Karen Stewart, RRT, and Anna Parkman, MBA, RRT.

**Contact:** For more information, contact Eric Hawkins at (304) 327-1754.

### March 15-17—Lake Tahoe, Nevada

The Greater Bay Area Chapter of the California Society for Respiratory Care host their 21st annual conference at Caesars Lake Tahoe. "Tahoe 2000" will offer 12 hours of continuing education credit.

**Contact:** For more information, call (925) 866-6643 or access their web site at [www.csrc.org](http://www.csrc.org).

### April 13-14—King of Prussia, Pennsylvania

The Pennsylvania Society for Respiratory Care presents their Third Annual Eastern Regional

Conference and Exhibition at the Holiday Inn. "Diversity, Dimension, Design 2000" will feature speakers William J. Malley, MS, RRT, and AARC President Garry W. Kauffman, MPA, RRT. Ten CEUs are pending. **Contact:** Angie Herstine at (609) 784-0340, or Ann Cusano at (215) 646-7300, ext. 428.

### May 19—Brainerd, Minnesota

The Minnesota Society for Respiratory Care host their Spring Fling — "Rev It Up" at the Breezy Point Resort. Five CRCEs will be requested. **Contact:** For more information, contact Laurie Tomaszewski at (651) 232-1922, Carolyn Dunow at [dunowc@fhpcare.com](mailto:dunowc@fhpcare.com), or Carl Mottram at [mottram.carl@mayo.edu](mailto:mottram.carl@mayo.edu).

### September 20-22—Rochester, Minnesota

The Minnesota Society for Respiratory Care host their 31st Annual Fall State Conference — "Too Hot to Handle." **Contact:** For more information, contact Laurie Tomaszewski at (651) 232-1922, Carolyn Dunow at [dunowc@fhpcare.com](mailto:dunowc@fhpcare.com), or Carl Mottram at [mottram.carl@mayo.edu](mailto:mottram.carl@mayo.edu).

## Other Meetings

### February 27-March 2—Keystone Resorts, Colorado

The 16th Annual Children's National Medical Center Symposium on ECMO and Advanced Therapies for Respiratory Failure will be held at Keystone Resorts. Topics include new uses for ECMO, hyperthermia for cancer therapy, hypothermia for neuroprotection, and extracorporeal CPR.

**Contact:** Dr. Billie Lou Short at (202) 884-5018 or [bshort@cnmc.org](mailto:bshort@cnmc.org).

### March 27-30—Clearwater Beach, Florida

All Children's Hospital will host a neonatal/pediatric transport conference, "Leading the Way — Staying Patient Focused," at the Hilton Clearwater Beach Resort. Continuing education hours available for RNs and RTs.

**Contact:** Connie Spadaccino at (800) 456-4543, ext. 4240, or fax (727) 892-4399.

### April 1-7—Miami, Florida

Miami Children's Hospital and the Ventilation Assisted Children's Center (VACC) are hosting their annual camp for ventilation-assisted children and their families. The campsite is A.D. Barnes Park, a 62-acre park located two miles from Miami Children's Hospital. Facilities include an air-conditioned lodge, two air-conditioned bunkhouses, and wheelchair-accessible swimming pool, playground, and nature trail. The VACC Camp treats families with children dependent on oxygen, a tracheostomy, ventilator, CPAP, or bi-level PAP to a week of fun and adventure in the company of their peers.

**Contact:** If you know of eligible, interested families, have them contact Camp Director Dr. Moises Simpeer or Bela Floretin at (305) 662-8380, ext. 4610, or (305) 662-8222. Applications will be accepted through Jan. 15, 2000.

### May 19-21—Atlanta, Georgia

Children's Healthcare of Atlanta-Egleston will sponsor "Moving ECMO into the New Millennium" — SEECMO 2000, the 10th Annual Southeastern ECMO Conference, at the Grand Hyatt Buckhead. Presentations will cover adult ECMO, ECMO flow direction, CVVH techniques, and hands-on water drills.

**Contact:** Micheal Heard, RN, at (404) 315-2593 or [micheal.heard@choa.org](mailto:micheal.heard@choa.org).

## MEMBERSHIP APPLICATION

Please read the eligibility requirements for each of the classifications in the right-hand column, then complete the applicable section. All information requested below must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

- ☐ Active Associate
- ☐ Foreign
- ☐ Physician
- ☐ Industrial
- ☐ Special
- ☐ Student

Last Name \_\_\_\_\_

First Name \_\_\_\_\_

Social Security No. \_\_\_\_\_

Home Address \_\_\_\_\_

City \_\_\_\_\_

State \_\_\_\_\_ Zip \_\_\_\_\_

Phone No. ( \_\_\_\_\_ ) \_\_\_\_\_

### Primary Job Responsibility (check one only)

- ☐ Technical Director
- ☐ Assistant Technical Director
- ☐ Pulmonary Function Specialist
- ☐ Instructor/Educator
- ☐ Supervisor
- ☐ Staff Therapist
- ☐ Staff Technician
- ☐ Rehabilitation/Home Care
- ☐ Medical Director
- ☐ Sales
- ☐ Student
- ☐ Other, specify \_\_\_\_\_

### Type of Business

- ☐ Hospital
- ☐ Skilled Nursing Facility
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Educational Institution
- ☐ Manufacturer or supplier
- ☐ Other, specify \_\_\_\_\_

Date of Birth (optional) \_\_\_\_\_ Sex (optional) \_\_\_\_\_

U.S. Citizen? \_\_\_\_ Yes \_\_\_\_ No

Have you ever been a member of the AARC? \_\_\_\_\_

If so, when? From \_\_\_\_\_ to \_\_\_\_\_



Preferred mailing address: ☐ Home ☐ Business

For office use only

### FOR ACTIVE MEMBER

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC. An individual who is an AARC Active Member in good standing on December 8, 1994, will continue as such provided his/her membership remains in good standing.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_

State \_\_\_\_\_ Zip \_\_\_\_\_

Phone No. ( \_\_\_\_\_ ) \_\_\_\_\_

Medical Director/Medical Sponsor \_\_\_\_\_

### FOR ASSOCIATE OR SPECIAL MEMBER

Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_

State \_\_\_\_\_ Zip \_\_\_\_\_

Phone No. ( \_\_\_\_\_ ) \_\_\_\_\_

### FOR STUDENT MEMBER

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

School/RC Program \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_

State \_\_\_\_\_ Zip \_\_\_\_\_

Phone No. ( \_\_\_\_\_ ) \_\_\_\_\_

### Length of program

- ☐ 1 year ☐ 4 years
- ☐ 2 years ☐ Other, specify \_\_\_\_\_

### Expected Date of Graduation (REQUIRED INFORMATION)

Month \_\_\_\_\_ Year \_\_\_\_\_

# American Association for Respiratory Care **MEMBERSHIP APPLICATION**

## Demographic Questions

We request that you answer these questions in order to help us design services and programs to meet your needs.

### Check the Highest Degree Earned

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

### Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

### Job Status

- ☐ Full Time
- ☐ Part Time

### Credentials

- ☐ RRT
- ☐ CRT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

### Salary

- ☐ Less than \$10,000
- ☐ \$10,001-\$20,000
- ☐ \$20,001-\$30,000
- ☐ \$30,001-\$40,000
- ☐ \$40,000 or more

### PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

A yearly subscription to RESPIRATORY CARE journal and AARC Times magazine includes an allocation of \$11.50 from my dues for each of these publications.

NOTE: Contributions or gifts to the AARC are not tax deductible as charitable contributions for income tax purposes. However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result of association lobbying activities. The AARC estimates that the nondeductible portion of your dues — the portion which is allocable to lobbying — is 26%.

Signature \_\_\_\_\_

Date \_\_\_\_\_

## Membership Fees

Payment must accompany your application to the AARC. Fees are for 12 months. (NOTE: Renewal fees are \$75.00 Active, Associate-Industrial or Associate-Physician, or Special status; \$90.00 for Associate-Foreign status; and \$45.00 for Student status).

- |                                                              |          |
|--------------------------------------------------------------|----------|
| <input type="checkbox"/> Active                              | \$ 87.50 |
| <input type="checkbox"/> Associate (Industrial or Physician) | \$ 87.50 |
| <input type="checkbox"/> Associate (Foreign)                 | \$102.50 |
| <input type="checkbox"/> Special                             | \$ 87.50 |
| <input type="checkbox"/> Student                             | \$ 45.00 |

TOTAL \$ \_\_\_\_\_

### Specialty Sections

Established to recognize the specialty areas of respiratory care, these sections publish a bi-monthly newsletter that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

- |                                                                 |         |
|-----------------------------------------------------------------|---------|
| <input type="checkbox"/> Adult Acute Care Section               | \$15.00 |
| <input type="checkbox"/> Education Section                      | \$20.00 |
| <input type="checkbox"/> Perinatal-Pediatric Section            | \$15.00 |
| <input type="checkbox"/> Diagnostics Section                    | \$15.00 |
| <input type="checkbox"/> Continuing Care-Rehabilitation Section | \$15.00 |
| <input type="checkbox"/> Management Section                     | \$20.00 |
| <input type="checkbox"/> Transport Section                      | \$15.00 |
| <input type="checkbox"/> Home Care Section                      | \$15.00 |
| <input type="checkbox"/> Subacute Care Section                  | \$15.00 |

TOTAL \$ \_\_\_\_\_

**GRAND TOTAL = Membership Fee  
plus optional sections \$ \_\_\_\_\_**

- ☐ Total Amount Enclosed/Charged \$ \_\_\_\_\_
- ☐ Please charge my dues (see below)

To charge your dues, complete the following:

- ☐ MasterCard
- ☐ Visa



Card Number \_\_\_\_\_

Card Expires \_\_\_\_/\_\_\_\_

Signature \_\_\_\_\_

Mail application and appropriate fees to:

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • [972] 243-2272 • Fax [972] 484-2720

# MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting  
by health professionals of adverse  
events and product problems

Form Approved: OMB No. 0910-0291 Expires: 4/31  
See OMB statement on rev

FDA Use Only (Resp Care)

Triage unit  
sequence #

Page \_\_\_\_ of \_\_\_\_

## A. Patient information

|                       |                                                              |                                                                            |                                         |
|-----------------------|--------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------|
| 1. Patient identifier | 2. Age at time of event:<br>or _____<br>Date of birth: _____ | 3. Sex<br><input type="checkbox"/> female<br><input type="checkbox"/> male | 4. Weight<br>____ lbs<br>or<br>____ kgs |
|-----------------------|--------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------|

In confidence

## B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event  
(check all that apply)

☐ death \_\_\_\_\_  
(mo/day/yr)

☐ life-threatening

☐ hospitalization - initial or prolonged

☐ disability

☐ congenital anomaly

☐ required intervention to prevent  
permanent impairment/damage

☐ other: \_\_\_\_\_

3. Date of event  
(mo/day/yr)

4. Date of this report  
(mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

## C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1

#2

2. Dose, frequency & route used

#1

#2

3. Therapy dates (if unknown, give duration)  
from/to (or best estimate)

#1

#2

4. Diagnosis for use (indication)

#1

#2

5. Event abated after use  
stopped or dose reduced

#1 ☐ yes ☐ no ☐ does not apply

#2 ☐ yes ☐ no ☐ does not apply

6. Lot # (if known)

#1

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after  
reintroduction

#1 ☐ yes ☐ no ☐ does not apply

#2 ☐ yes ☐ no ☐ does not apply

9. NDC # (for product problems only)

#1

#2

10. Concomitant medical products and therapy dates (exclude treatment of event)

## D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device

☐ health professional

☐ lay user/patient

☐ other: \_\_\_\_\_

6.

model # \_\_\_\_\_

catalog # \_\_\_\_\_

serial # \_\_\_\_\_

lot # \_\_\_\_\_

other # \_\_\_\_\_

5. Expiration date  
(mo/day/yr)

7. If implanted, give date  
(mo/day/yr)

8. If explanted, give date  
(mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)

☐ yes ☐ no

☐ returned to manufacturer on \_\_\_\_\_  
(mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

## E. Reporter (see confidentiality section on back)

1. Name & address

phone #

2. Health professional?

☐ yes ☐ no

3. Occupation

4. Also reported to

☐ manufacturer

☐ user facility

☐ distributor

5. If you do NOT want your identity disclosed to  
the manufacturer, place an "X" in this box. ☐



Mail to: MEDWATCH  
5600 Fishers Lane  
Rockville, MD 20852-9787

or FAX to:  
1-800-FDA-0178

# ADVICE ABOUT VOLUNTARY REPORTING

## Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

## Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

## Report even if:

- you're not certain the product caused the event
- you don't have all the details

## Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

## How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

## Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

**If your report involves a serious adverse event with a device** and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

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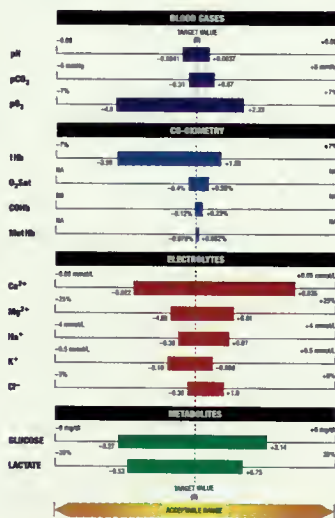
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